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(54) **Title:** SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME

**(57) Abstract**
The present invention is directed to novel polypeptides and to nucleic acid molecules encoding those polypeptides. Also provided herein are vectors and host cells comprising those nucleic acid sequences, chimeric polypeptide molecules comprising the polypeptides of the present invention fused to heterologous polypeptide sequences, antibodies which bind to the polypeptides of the present invention and to methods for producing the polypeptides of the present invention.

SECRETED AND POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME FIELD OF THE INVENTION The present invention relates generally to the identification and isolation of novel DNA and to the recombinant production of novel polypeptides.

BACKGROUND OF THE INVENTION Extracellular proteins play important roles in, among other things, the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e. g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment.

Secreted proteins have various industrial applications, including as pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other are secretory proteins.

Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents. Efforts are being undertaken by both industry and academia to identify new, native secreted proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., Proc. Natl. Acad. Sci. 93 : (1996) ; U. S. Patent No. 5, 536,

Membrane-bound proteins and receptors can play important roles in, among other things, the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e. g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins.

Such membrane-bound proteins and cell receptors include, but are not limited to, receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesin molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interactions. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Efforts are being undertaken by both industry and academia to identify new, native receptor or membrane-bound proteins. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel receptor or membrane-bound proteins.

SUMMARY OF THE INVENTION In one embodiment, the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence that encodes a PRO polypeptide.

In one aspect, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about nucleic acid sequence identity, alternatively at least about nucleic acid sequence identity, alternatively at least about nucleic acid sequence identity, alternatively at least about 83 % nucleic acid sequence identity, alternatively at least about nucleic acid sequence identity, alternatively at least about nucleic acid sequence identity, alternatively at least about nucleic acid sequence identity, alternatively at least about nucleic acid sequence identity, alternatively at least about 88 % nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93 % nucleic acid sequence identity, alternatively at least about nucleic acid sequence identity, alternatively at least about 95 % nucleic acid sequence identity, alternatively at least about nucleic acid sequence identity, alternatively at least about nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99% nucleic acid sequence identity to (a) a DNA molecule encoding a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In other aspects, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80 % nucleic acid sequence identity, alternatively at least about 81 % nucleic acid sequence identity, alternatively at least about nucleic acid sequence identity, alternatively at least about 83 % nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86 % nucleic acid sequence identity, alternatively at least about 87 % nucleic acid sequence identity, alternatively at least about % nucleic acid sequence identity, alternatively at least about 89% nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about 91% nucleic acid sequence identity, alternatively at least about 92% nucleic acid sequence identity, alternatively at least about 93 % nucleic acid sequence identity, alternatively at least about nucleic acid sequence identity, alternatively at least about 95 % nucleic acid sequence identity, alternatively at least about 96% nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98 % nucleic acid sequence identity and alternatively at least about 99 % nucleic acid' sequence identity to (a) a DNA molecule comprising the coding sequence of a full-length PRO polypeptide cDNA as disclosed herein, the coding sequence of a PRO polypeptide lacking the signal peptide as disclosed herein, the coding sequence of an extracellular domain of a transmembrane PRO polypeptide, with or without the signal peptide, as disclosed herein or the coding sequence of any other specifically defined fragment of the full-length amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In a further aspect, the invention concerns an isolated nucleic acid molecule comprising a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81 % nucleic acid sequence identity, alternatively at least about nucleic acid sequence identity, alternatively at least about 83 % nucleic acid sequence identity, alternatively at least about 84 % nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87% nucleic acid sequence identity, alternatively at least about 88% nucleic acid sequence identity, alternatively at least about nucleic acid sequence identity, alternatively at least about nucleic acid sequence identity, alternatively at least about 91 % nucleic acid sequence identity, alternatively at least about nucleic acid sequence identity, alternatively at least about nucleic acid sequence identity, alternatively at least about nucleic acid sequence identity, alternatively at least about nucleic acid sequence identity, alternatively at least about nucleic acid sequence identity, alternatively at least about nucleic acid sequence identity, alternatively at least about nucleic acid sequence identity and alternatively at least about nucleic acid sequence identity

to (a) a DNA molecule that encodes the same mature polypeptide encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein, or (b) the complement of the DNA molecule of (a).

Another aspect the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence encoding a PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated, or is complementary to such encoding nucleotide sequence, wherein the transmembrane domain (s) of such polypeptide are disclosed herein. Therefore, soluble extracellular domains of the herein described PRO polypeptides are contemplated.

Another embodiment is directed to fragments of a PRO polypeptide coding sequence, or the complement thereof, that may find use as, for example, hybridization probes, for encoding fragments of a PRO polypeptide that may optionally encode a polypeptide comprising a binding site for an anti-PRO antibody or as antisense oligonucleotide probes. Such nucleic acid fragments are usually at least about 10 nucleotides in length, alternatively at least about 15 nucleotides in length, alternatively at least about 20 nucleotides in length, alternatively at least about 30 nucleotides in length, alternatively at least about 40 nucleotides in length, alternatively at least about 50 nucleotides in length, alternatively at least about 60 nucleotides in length, alternatively at least about 70 nucleotides in length, alternatively at least about nucleotides in length, alternatively at least about 90 nucleotides in length, alternatively at least about 100 nucleotides in length, alternatively at least about 110 nucleotides in length, alternatively at least about 120 nucleotides in length, alternatively at least about 130 nucleotides in length, alternatively at least about 140 nucleotides in length, alternatively at least about 150 nucleotides in length, alternatively at least about 160 nucleotides in length, alternatively at least about 170 nucleotides in length, alternatively at least about 180 nucleotides in length, alternatively at least about 190 nucleotides in length, alternatively at least about 200 nucleotides in length, alternatively at least about 250 nucleotides in length, alternatively at least about 300 nucleotides in length, alternatively at least about 350 nucleotides in length, alternatively at least about 400 nucleotides in length, alternatively at least about 450 nucleotides in length, alternatively at least about 500 nucleotides in length, alternatively at least about 600 nucleotides in length, alternatively at least about 700 nucleotides in length, alternatively at least about 800 nucleotides in length, alternatively at least about 900 nucleotides in length and alternatively at least about 1000 nucleotides in length, wherein in this context the term"about"means the referenced nucleotide sequence length plus or minus 10% of that referenced length. It is noted that novel fragments of a PRO polypeptide-encoding nucleotide sequence may be determined in a routine manner by aligning the PRO polypeptide-encoding nucleotide sequence with other known nucleotide sequences using any of a number of well known sequence alignment programs and determining which PRO polypeptide-encoding nucleotide sequence fragment (s) are novel. All of such PRO polypeptide-encoding nucleotide sequences are contemplated herein. Also contemplated are the PRO polypeptide fragments encoded by these nucleotide molecule fragments, preferably those PRO polypeptide fragments that comprise a binding site for an anti-PRO antibody.

In another embodiment, the invention provides isolated PRO polypeptide encoded by any of the isolated nucleic acid sequences hereinabove identified.

In a certain aspect, the invention concerns an isolated PRO polypeptide, comprising an amino acid sequence having at least about amino acid sequence identity, alternatively at least about amino acid sequence identity, alternatively at least about amino acid sequence identity, alternatively at least about 83 % amino acid sequence identity, alternatively at least about 84 % amino acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 87% amino acid sequence identity, alternatively at least about 88% amino acid sequence identity, alternatively at least about acid sequence identity, alternatively at least about amino acid sequence identity, alternatively at least about acid sequence

identity, alternatively at least about 92% amino acid sequence identity, alternatively at least about 93% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 96% amino acid sequence identity, alternatively at least about amino acid sequence identity, alternatively at least about 98 % amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to a PRO polypeptide having a full-length amino acid sequence as disclosed herein, an amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane protein, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of the full-length amino acid sequence as disclosed herein.

In a further aspect, the invention concerns an isolated PRO polypeptide comprising an amino acid sequence having at least about acid sequence identity, alternatively at least about 81% amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about 83 % amino acid sequence identity, alternatively at least about acid sequence identity, alternatively at least about 85% amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about acid sequence identity, alternatively at least about 88% amino acid sequence identity, alternatively at least about 89% amino acid sequence identity, alternatively at least about amino acid sequence identity, alternatively at least about 91 % amino acid sequence identity, alternatively at least about 92% amino acid sequence identity, alternatively at least about 93% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about 95% amino acid sequence identity, alternatively at least about 96 % amino acid sequence identity, alternatively at least about 97 % amino acid sequence identity, alternatively at least about 98% amino acid sequence identity and alternatively at least about 99% amino acid sequence identity to an amino acid sequence encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein.

In a specific aspect, the invention provides an isolated PRO polypeptide without the N-terminal signal sequence and/or the initiating methionine and is encoded by a nucleotide sequence that encodes such an amino acid sequence as hereinbefore described. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

Another aspect the invention provides an isolated PRO polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the PRO polypeptide and recovering the PRO polypeptide from the cell culture.

In yet another embodiment, the invention concerns agonists and antagonists of a native PRO polypeptide as defined herein. In a particular embodiment, the agonist or antagonist is an anti-PRO antibody or a small molecule.

In a further embodiment, the invention concerns a method of identifying agonists or antagonists to a PRO polypeptide which comprise contacting the PRO polypeptide with a candidate molecule and monitoring a biological activity mediated by said PRO polypeptide. Preferably, the PRO polypeptide is a native PRO polypeptide.

In a still further embodiment, the invention concerns a composition of matter comprising a PRO polypeptide, or an agonist or antagonist of a PRO polypeptide as herein described, or an anti-PRO antibody, in combination with a carrier. Optionally, the carrier is a pharmaceutically acceptable carrier.

Another embodiment of the present invention is directed to the use of a PRO polypeptide, or an agonist or antagonist thereof as hereinbefore described, or an anti-PRO antibody, for the preparation of a medicament useful in the treatment of a condition which is responsive to the PRO polypeptide, an agonist or antagonist thereof or an anti-PRO antibody.

In other embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the herein described polypeptides. Host cell comprising any such vector are also provided. By way of example, the host cells may be CHO cells, E. coli, or yeast. A process for producing any of the herein described polypeptides is further provided and comprises culturing host cells under conditions suitable for expression of the desired polypeptide and recovering the desired polypeptide from the cell culture.

In other embodiments, the invention provides chimeric molecules comprising any of the herein described polypeptides fused to a heterologous polypeptide or amino acid sequence. Example of such chimeric molecules comprise any of the herein described polypeptides fused to an epitope tag sequence or a Fc region of an immunoglobulin.

In another embodiment, the invention provides an antibody which binds, preferably specifically, to any of the above or below described polypeptides. Optionally, the antibody is a monoclonal antibody, humanized antibody, antibody fragment or single-chain antibody.

In yet other embodiments, the invention provides oligonucleotide probes which may be useful for isolating genomic and cDNA nucleotide sequences, measuring or detecting expression of an associated gene or as antisense probes, wherein those probes may be derived from any of the above or below described nucleotide sequences. Preferred probe lengths are described above.

In yet other embodiments, the present invention is directed to methods of using the PRO polypeptides of the present invention for a variety of uses based upon the functional biological assay data presented in the Examples below.

BRIEF DESCRIPTION OF THE DRAWINGS Figure 1 shows a nucleotide sequence (SEQ ID NO : 1) of a native sequence PR0276 cDNA, wherein SEQ ID NO : is a clone designated herein as"DNA16435-1208".

Figure 2 shows the amino acid sequence (SEQ ID NO : 2) derived from the coding sequence of SEQ ID NO : 1 shown in Figure 1.

Figure 3 shows a nucleotide sequence (SEQ ID NO : 3) of a native sequence PR0284 cDNA, wherein SEQ ID NO : 3 is a clone designated herein as"DNA23318-1211".

Figure 4 shows the amino acid sequence (SEQ ID NO : 4) derived from the coding sequence of SEQ ID NO : 3 shown in Figure 3.

Figure 5 shows a nucleotide sequence (SEQ ID NO : of a native sequence PRO 193 cDNA, wherein SEQ ID NO : is a clone designated herein as"DNA23322-1393".

Figure 6 shows the amino acid sequence (SEQ ID NO : 6) derived from the coding sequence of SEQ ID NO : shown in Figure 5.

Figure 7 shows a nucleotide sequence (SEQ ID NO : 7) of a native sequence cDNA, wherein SEQ ID

NO : 7 is a clone designated herein as"DNA23334-1392".

Figure 8 shows the amino acid sequence (SEQ ID NO : 8) derived from the coding sequence of SEQ ID NO : 7 shown in Figure 7.

Figure 9 shows a nucleotide sequence (SEQ ID NO : 9) of a native sequence wherein SEQ ID NO : 9 is a clone designated herein as"DNA26843-1389".

Figure 10 shows the amino acid sequence (SEQ ID NO : 10) derived from the coding sequence of SEQ ID : 9 shown in Figure 9.

Figure 11 shows a nucleotide sequence (SEQ ID NO : 11) of a native sequence wherein SEQ ID NO : 11 is a clone designated herein as"DNA26844-1394".

Figure 12 shows the amino acid sequence (SEQ ID NO : 12) derived from the coding sequence of SEQ ID NO : 11 shown in Figure 11.

Figure 13 shows a nucleotide sequence (SEQ ID NO : 13) of a native sequence PR0218 cDNA, wherein SEQ ID NO : 13 is a clone designated herein

Figure 14 shows the amino acid sequence (SEQ ID NO : 14) derived from the coding sequence of SEQ ID NO : 13 shown in Figure 13.

Figure 15 shows a nucleotide sequence (SEQ ID NO : 15) of a native sequence PR0260 cDNA, wherein SEQ ID NO : 15 is a clone designated herein as"DNA33470-1175".

Figure 16 shows the amino acid sequence (SEQ ID NO : 16) derived from the coding sequence of SEQ ID NO : 15 shown in Figure 15.

Figure 17 shows a nucleotide sequence (SEQ ID NO : 17) of a native sequence PR0233 cDNA, wherein SEQ ID NO : 17 is a clone designated herein as"DNA34436-1238".

Figure 18 shows the amino acid sequence (SEQ ID NO : 18) derived from the coding sequence of SEQ ID NO : 17 shown in Figure 17.

Figure 19 shows a nucleotide sequence (SEQ ID NO : 19) of a native sequence PR0234 cDNA, wherein SEQ ID NO : 19 is a clone designated herein as"DNA35557-1137".

Figure 20 shows the amino acid sequence (SEQ ID NO : 20) derived from the coding sequence of SEQ ID NO : 19 shown in Figure 19.

Figure 21 shows a nucleotide sequence (SEQ ID NO : 21) of a native sequence PR0236 cDNA, wherein SEQ ID NO : 21 is a clone designated herein as"DNA35599-1168".

Figure 22 shows the amino acid sequence (SEQ ID NO : 22) derived from the coding sequence of SEQ ID NO : 21 shown in Figure 21.

Figure 23 shows a nucleotide sequence (SEQ ID NO : 23) of a native sequence PR0244 cDNA, wherein SEQ ID NO : 23 is a clone designated herein as"DNA35668-1171".

Figure 24 shows the amino acid sequence (SEQ ID NO : 24) derived from the coding sequence of SEQ ID NO : 23 shown in Figure 23.

Figure 25 shows a nucleotide sequence (SEQ ID NO : 25) of a native sequence PR0262 cDNA, wherein SEQ ID NO : 25 is a clone designated herein

Figure 26 shows the amino acid sequence (SEQ ID NO : 26) derived from the coding sequence of SEQ ID NO : 25 shown in Figure 25.

Figure 27 shows a nucleotide sequence (SEQ ID NO : 27) of a native sequence PR0271 cDNA, wherein SEQ ID NO : 27 is a clone designated herein as"DNA39423-1182".

Figure 28 shows the amino acid sequence (SEQ ID NO : 28) derived from the coding sequence of SEQ ID NO : 27 shown in Figure 27.

Figure 29 shows a nucleotide sequence (SEQ ID NO : 29) of a native sequence PR0268 cDNA, wherein SEQ ID NO : 29 is a clone designated herein

Figure 30 shows the amino acid sequence (SEQ ID NO : 30) derived from the coding sequence of SEQ ID NO : 29 shown in Figure 29.

Figure 31 shows a nucleotide sequence (SEQ ID NO : of a native sequence PR0270 cDNA, wherein SEQ ID NO : 31 is a clone designated herein as"DNA39510-1181".

Figure 32 shows the amino acid sequence (SEQ ID NO : 32) derived from the coding sequence of SEQ ID NO : 31 shown in Figure

Figure 33 shows a nucleotide sequence (SEQ ID NO : 33) of a native sequence PR0355 cDNA, wherein SEQ ID NO : 33 is a clone designated herein as"DNA39518-1247".

Figure 34 shows the amino acid sequence (SEQ ID NO : 34) derived from the coding sequence of SEQ ID NO : 33 shown in Figure 33.

Figure 35 shows a nucleotide sequence (SEQ ID NO : 35) of a native sequence PR0298 cDNA, wherein SEQ ID NO : 35 is a clone designated herein as"DNA39975-1210".

Figure 36 shows the amino acid sequence (SEQ ID NO : 36) derived from the coding sequence of SEQ ID NO : 35 shown in Figure 35.

Figure 37 shows a nucleotide sequence (SEQ ID NO : 37) of a native sequence PR0299 cDNA, wherein SEQ ID NO : 37 is a clone designated herein as"DNA39976-1215".

Figure 38 shows the amino acid sequence (SEQ ID NO : 38) derived from the coding sequence of SEQ ID NO : 37 shown in Figure 37.

Figure 39 shows a nucleotide sequence (SEQ ID NO : 39) of a native sequence PR0296 cDNA, wherein SEQ ID NO : 39 is a clone designated herein

Figure 40 shows the amino acid sequence (SEQ ID NO : 40) derived from the coding sequence of SEQ ID NO : 39 shown in Figure 39.

Figure 41 shows a nucleotide sequence (SEQ ID NO : 41) of a native sequence wherein SEQ ID NO : 41 is a clone designated herein as"DNA40594-1233".

Figure 42 shows the amino acid sequence (SEQ ID NO : 42) derived from the coding sequence of SEQ ID NO : 41 shown in Figure 41.

Figure 43 shows a nucleotide sequence (SEQ ID NO : 43) of a native sequence PR0330 cDNA, wherein SEQ ID NO : 43 is a clone designated herein as"DNA40603-1232".

Figure 44 shows the amino acid sequence (SEQ ID NO : 44) derived from the coding sequence of SEQ ID NO : 43 shown in Figure 43.

Figure 45 shows a nucleotide sequence (SEQ ID NO : 45) of a native sequence PR0294 cDNA, wherein SEQ ID NO : 45 is a clone designated herein as"DNA40604-1187".

Figure 46 shows the amino acid sequence (SEQ ID NO : 46) derived from the coding sequence of SEQ ID NO : 45 shown in Figure 45.

Figure 47 shows a nucleotide sequence (SEQ ID NO : 47) of a native sequence PR0300 cDNA, wherein SEQ ID NO : 47 is a clone designated herein as"DNA40625-1189".

Figure 48 shows the amino acid sequence (SEQ ID NO : 48) derived from the coding sequence of SEQ ID NO : 47 shown in Figure 47.

Figure 49 shows a nucleotide sequence (SEQ ID NO : 49) of a native sequence PR0307 cDNA, wherein SEQ ID NO : 49 is a clone designated herein

Figure 50 shows the amino acid sequence (SEQ ID NO : 50) derived from the coding sequence of SEQ ID NO : 49 shown in Figure 49.

Figure 51 shows a nucleotide sequence (SEQ ID NO : of a native sequence PR0334 cDNA, wherein SEQ ID NO : 51 is a clone designated herein as"DNA41379-1236".

Figure 52 shows the amino acid sequence (SEQ ID NO : 52) derived from the coding sequence of SEQ ID NO : 51 shown in Figure

Figure 53 shows a nucleotide sequence (SEQ ID NO : 53) of a native sequence PR0352 cDNA, wherein SEQ ID NO : 53 is a clone designated herein as"DNA41386-1316".

Figure 54 shows the amino acid sequence (SEQ ID NO : 54) derived from the coding sequence of SEQ ID NO : 53 shown in Figure 53.

Figure 55 shows a nucleotide sequence (SEQ ID NO : 55) of a native sequence PR0710 cDNA, wherein SEQ ID NO : 55 is a clone designated herein as"DNA44161-1434".

Figure 56 shows the amino acid sequence (SEQ ID NO : 56) derived from the coding sequence of SEQ ID NO : 55 shown in Figure 55.

Figure 57 shows a nucleotide sequence : 57) of a native sequence PR0873 cDNA, wherein SEQ ID NO : 57 is a clone designated herein as"DNA44179-1362".

Figure 58 shows the amino acid sequence (SEQ ID NO : 58) derived from the coding sequence of SEQ ID NO : 57 shown in Figure 57.

Figure 59 shows a nucleotide sequence (SEQ ID NO : 59) of a native sequence PR0354 cDNA, wherein SEQ ID NO : 59 is a clone designated herein as"DNA44192-1246".

Figure 60 shows the amino acid sequence (SEQ ID NO : 60) derived from the coding sequence of SEQ ID NO : 59 shown in Figure 59.

Figure 61 shows a nucleotide sequence (SEQ ID NO : 61) of a native sequence cDNA, wherein SEQ ID NO : 61 is a clone designated herein as"DNA44694-1500".

Figure 62 shows the amino acid sequence (SEQ ID NO : 62) derived from the coding sequence of SEQ ID NO : 61 shown in Figure 61.

Figure 63 shows a nucleotide sequence (SEQ ID NO : 63) of a native sequence PR0382 cDNA, wherein : 63 is a clone designated herein as"DNA45234-1277".

Figure 64 shows the amino acid sequence (SEQ ID NO : 64) derived from the coding sequence of SEQ ID NO : 63 shown in Figure 63.

Figure 65 shows a nucleotide sequence (SEQ ID NO : 65) of a native sequence wherein SEQ ID NO : 65 is a clone designated herein

Figure 66 shows the amino acid sequence (SEQ ID NO : 66) derived from the coding sequence of SEQ ID NO : 65 shown in Figure 65.

Figure 67 shows a nucleotide sequence (SEQ ID NO : 67) of a native sequence PR0386 cDNA, wherein SEQ ID NO : 67 is a clone designated herein as"DNA45415-1318".

Figure 68 shows the amino acid sequence (SEQ ID NO : 68) derived from the coding sequence of SEQ ID NO : 67 shown in Figure 67.

Figure 69 shows a nucleotide sequence (SEQ ID NO : 69) of a native sequence PR0541 cDNA, wherein SEQ ID NO : 69 is a clone designated herein as"DNA45417-1432".

Figure 70 shows the amino acid sequence (SEQ ID NO : 70) derived from the coding sequence of SEQ ID NO : 69 shown in Figure 69.

Figure 71 shows a nucleotide sequence (SEQ ID NO : 71) of a native sequence PR0852 cDNA, wherein SEQ ID NO : 71 is a clone designated herein as"DNA45493-1349".

Figure 72 shows the amino acid sequence (SEQ ID NO : 72) derived from the coding sequence of SEQ ID NO : 71 shown in Figure 71.

Figure 73 shows a nucleotide sequence (SEQ ID NO : 73) of a native sequence PR0700 cDNA, wherein SEQ ID NO : 73 is a clone designated herein as"DNA46776-1284".

Figure 74 shows the amino acid sequence (SEQ ID NO : 74) derived from the coding sequence of SEQ ID NO : 73 shown in Figure 73.

Figures 75A-75B show a nucleotide sequence (SEQ ID NO : 75) of a native sequence PR0708 cDNA, wherein SEQ ID NO : 75 is a clone designated herein as"DNA48296-1292".

Figure 76 shows the amino acid sequence (SEQ ID NO : 76) derived from the coding sequence of SEQ ID NO : 75 shown in Figures 75A-75B.

Figure 77 shows a nucleotide sequence (SEQ ID NO : 77) of a native sequence PR0707 cDNA, wherein SEQ ID NO : 77 is a clone designated herein as"DNA48306-1291".

Figure 78 shows the amino acid sequence (SEQ ID NO : 78) derived from the coding sequence of SEQ ID NO : 77 shown in Figure 77.

Figure 79 shows a nucleotide sequence (SEQ ID NO : 79) of a native sequence PR0864 cDNA, wherein SEQ ID NO : 79 is a clone designated herein as"DNA48328-1355".

Figure 80 shows the amino acid sequence (SEQ ID NO : 80) derived from the coding sequence of SEQ ID NO : 79 shown in Figure 79.

Figure 81 shows a nucleotide sequence (SEQ ID NO : of a native sequence PR0706 cDNA, wherein SEQ ID NO : 81 is a clone designated herein as"DNA48329-1290".

Figure 82 shows the amino acid sequence (SEQ ID NO : 82) derived from the coding sequence of SEQ ID NO : 81 shown in Figure

Figure 83 shows a nucleotide sequence (SEQ ID NO : 83) of a native sequence PR0732 cDNA, wherein SEQ ID NO : 83 is a clone designated herein as"DNA48334-1435".

Figure 84 shows the amino acid sequence (SEQ ID NO : 84) derived from the coding sequence of SEQ ID NO : 83 shown in Figure 83.

Figure 85 shows a nucleotide sequence (SEQ ID NO : 85) of a native sequence PR0537 cDNA, wherein : 85 is a clone designated herein as"DNA49141-1431".

Figure 86 shows the amino acid sequence (SEQ ID NO : 86) derived from the coding sequence of SEQ ID NO : 85 shown in Figure 85.

Figure 87 shows a nucleotide sequence (SEQ ID NO : 87) of a native sequence PR0545 cDNA, wherein SEQ ID NO : 87 is a clone designated herein as"DNA49624-1279".

Figure 88 shows the amino acid sequence (SEQ ID NO : 88) derived from the coding sequence of SEQ ID NO : 87 shown in Figure 87.

Figure 89 shows a nucleotide sequence (SEQ ID NO : 89) of a native sequence PR0718 cDNA, wherein SEQ ID NO : 89 is a clone designated herein as"DNA49647-1398".

Figure 90 shows the amino acid sequence (SEQ ID NO : 90) derived from the coding sequence of SEQ ID NO : 89 shown in Figure 89.

Figure 91 shows a nucleotide sequence (SEQ ID NO : 91) of a native sequence PR0872 cDNA, wherein SEQ ID NO : 91 is a clone designated herein as"DNA49819-1439".

Figure 92 shows the amino acid sequence (SEQ ID NO : 92) derived from the coding sequence of SEQ ID NO : 91 shown in Figure 91.

Figure 93 shows a nucleotide sequence (SEQ ID NO : 93) of a native sequence PR0704 cDNA, wherein SEQ ID NO : 93 is a clone designated herein as"DNA50911-1288".

Figure 94 shows the amino acid sequence (SEQ ID NO : 94) derived from the coding sequence of SEQ ID NO : 93 shown in Figure 93.

Figure 95 shows a nucleotide sequence (SEQ ID NO : 95) of a native sequence PR0705 cDNA, wherein SEQ ID NO : 95 is a clone designated herein as"DNA50914-1289".

Figure 96 shows the amino acid sequence (SEQ ID NO : 96) derived from the coding sequence of SEQ ID NO : 95 shown in Figure 95.

Figure 97 shows a nucleotide sequence (SEQ ID NO : 97) of a native sequence PR0871 cDNA, wherein SEQ ID NO : 97 is a clone designated herein as"DNA50919-1361".

Figure 98 shows the amino acid sequence (SEQ ID NO : 98) derived from the coding sequence of SEQ ID NO : 97 shown in Figure 97.

Figure 99 shows a nucleotide sequence (SEQ ID NO : 99) of a native sequence PR0702 cDNA, wherein SEQ ID NO : 99 is a clone designated herein

Figure 100 shows the amino acid sequence (SEQ ID NO : 100) derived from the coding sequence of SEQ ID NO : 99 shown in Figure 99.

Figure 101 shows sequence (SEQ ID NO : 101) of a native sequence PR0944 cDNA, wherein SEQ ID NO : 101 is a clone designated herein as"DNA52185-1370".

Figure 102 shows the amino acid sequence (SEQ ID NO : 102) derived from the coding sequence of SEQ ID NO : 101 shown in Figure 101.

Figure 103 shows a nucleotide sequence (SEQ ID NO : 103) of a native sequence PR0739 cDNA, wherein SEQ ID NO : 103 is a clone designated herein as"DNA52756".

Figure 104 shows the amino acid sequence (SEQ ID NO : 104) derived from the coding sequence of SEQ ID NO : 103 shown in Figure 103.

Figure 105 shows a nucleotide sequence : 105) of a native sequence PR0941 cDNA, wherein SEQ ID NO : 105 is a clone designated herein as"DNA53906-1368".

Figure 106 shows the amino acid sequence (SEQ ID NO : 106) derived from the coding sequence of SEQ ID NO : 105 shown in Figure 105.

Figure 107 shows a nucleotide sequence (SEQ ID NO : 107) of a native sequence wherein SEQ ID NO : 107 is a clone designated herein as"DNA53912-1457".

Figure 108 shows the amino acid sequence (SEQ ID NO : 108) derived from the coding sequence of SEQ ID NO : 107 shown in Figure 107.

Figure 109 shows a nucleotide sequence (SEQ ID NO : 109) of a native sequence wherein SEQ ID NO : 109 is a clone designated herein as"DNA53913-1490".

Figure 110 shows the amino acid sequence (SEQ ID NO : 110) derived from the coding sequence of SEQ ID NO : 109 shown in Figure 109.

Figure 111 shows a nucleotide sequence (SEQ ID NO : 111) of a native sequence PR0983 cDNA, wherein SEQ ID NO : is a clone designated herein as"DNA53977-1371".

Figure 112 shows the amino acid sequence (SEQ ID NO : 112) derived from the coding sequence of SEQ ID NO : 111 shown in Figure

Figure 113 shows a nucleotide sequence (SEQ ID NO : 113) of a native sequence cDNA, wherein SEQ ID NO : 113 is a clone designated herein as"DNA53978-1443".

Figure 114 shows the amino acid sequence (SEQ ID NO : 114) derived from the coding sequence of SEQ ID NO : 113 shown in Figure 113.

Figure 115 shows a nucleotide sequence (SEQ ID NO : 115) of a native sequence PR0783 cDNA, wherein SEQ ID NO : 115 is a clone designated herein as"DNA53996-1442".

Figure 116 shows the amino acid sequence (SEQ ID NO : 116) derived from the coding sequence of SEQ ID NO : 115 shown in Figure 115.

Figure 117 shows a nucleotide sequence (SEQ ID NO : 117) of a native sequence PR0940 cDNA, wherein SEQ ID NO : 117 is a clone designated herein as"DNA54002-1367".

Figure 118 shows the amino acid sequence (SEQ ID NO : 118) derived from the coding sequence of SEQ ID NO : 117 shown in Figure 117.

Figure 119 shows a nucleotide sequence (SEQ ID NO : 119) of a native sequence PR0768 cDNA, wherein SEQ ID NO : is a clone designated herein as"DNA55737-1345".

Figure 120 shows the amino acid sequence (SEQ ID NO : 120) derived from the coding sequence of SEQ ID NO : shown in Figure 119.

Figure 121 shows a nucleotide sequence (SEQ ID NO : of a native sequence wherein SEQ ID NO : 121 is a clone designated herein as"DNA56050-1455".

Figure 122 shows the amino acid sequence (SEQ ID NO : 122) derived from the coding sequence of SEQ ID NO : 121 shown in Figure 121.

Figure 123 shows a nucleotide sequence (SEQ ID NO : 123) of a native sequence wherein SEQ ID NO : 123 is a clone designated herein as"DNA56052-1454".

Figure 124 shows the amino acid sequence (SEQ ID NO : 124) derived from the coding sequence of SEQ ID NO : 123 shown in Figure 123.

Figure 125 shows a nucleotide sequence (SEQ ID NO : 125) of a native sequence cDNA, wherein SEQ ID NO : 125 is a clone designated herein as"DNA56107-1415".

Figure 126 shows the amino acid sequence (SEQ ID NO : 126) derived from the coding sequence of SEQ ID NO : 125 shown in Figure 125.

Figure 127 shows a nucleotide sequence (SEQ ID NO : 127) of a native sequence PR0793 cDNA, wherein SEQ ID NO : 127 is a clone designated herein as"DNA56110-1437".

Figure 128 shows the amino acid sequence (SEQ ID NO : 128) derived from the coding sequence of SEQ ID NO : 127 shown in Figure 127.

Figure 129 shows a nucleotide sequence (SEQ ID NO : 129) of a native sequence wherein SEQ ID NO : 129 is a clone designated herein as DNA56406-1704 Figure 130 shows the amino acid sequence (SEQ ID NO : 130) derived from the coding sequence of SEQ ID NO : 129 shown in Figure 129.

Figure 131 shows a nucleotide sequence (SEQ ID NO : of a native sequence wherein SEQ ID NO : 131 is a clone designated herein as"DNA56409-1377".

Figure 132 shows the amino acid sequence (SEQ ID NO : 132) derived from the coding sequence of SEQ ID NO : 131 shown in Figure

Figure 133 shows a nucleotide sequence (SEQ ID NO : 133) of a native sequence cDNA, wherein SEQ ID NO : 133 is a clone designated herein as"DNA56410-1414".

Figure 134 shows the amino acid sequence (SEQ ID NO : 134) derived from the coding sequence of SEQ ID NO : 133 shown in Figure 133.

Figure 135 shows a nucleotide sequence (SEQ ID NO : 135) of a native sequence PR0937 cDNA, wherein SEQ ID NO : 135 is a clone designated herein as"DNA56436-1448".

Figure 136 shows the amino acid sequence (SEQ ID NO : 136) derived from the coding sequence of SEQ ID NO : 135 shown in Figure 135.

Figure 137 shows a nucleotide sequence (SEQ ID NO : 137) of a native sequence cDNA, wherein SEQ ID NO : 137 is a clone designated herein as"DNA56529-1647".

Figure 138 shows the amino acid sequence (SEQ ID NO : 138) derived from the coding sequence of SEQ ID NO : 137 shown in Figure 137.

Figure 139 shows a nucleotide sequence (SEQ ID NO : 139) of wherein SEQ ID NO : 139 is a clone designated herein as"DNA56855-1447".

Figure 140 shows the amino acid sequence (SEQ ID NO : 140) derived from the coding sequence of SEQ ID NO : 139 shown in Figure 139.

Figure 141 shows a nucleotide sequence (SEQ ID NO : 141) of a native sequence PR0839 cDNA, wherein SEQ ID NO : 141 is a clone designated herein as"DNA56859-1445".

Figure 142 shows the amino acid sequence (SEQ ID NO : 142) derived from the coding sequence of SEQ ID NO : 141 shown in Figure

Figure 143 shows a nucleotide sequence (SEQ ID NO : 143) of a native sequence wherein SEQ ID NO :

143 is a clone designated herein as"DNA56860-1510".

Figure 144 shows the amino acid sequence (SEQ ID NO : 144) derived from the coding sequence of SEQ ID NO : 143 shown in Figure 143.

Figure 145 shows a nucleotide sequence (SEQ ID NO : 145) of a native sequence cDNA, wherein SEQ ID NO : 145 is a clone designated herein

Figure 146 shows the amino acid sequence (SEQ ID NO : 146) derived from the coding sequence of SEQ ID NO : 145 shown in Figure 145.

Figure 147 shows a nucleotide sequence (SEQ ID NO : 147) of a native sequence wherein SEQ ID NO : 147 is a clone designated herein as"DNA56868-1478".

Figure shows the amino acid sequence (SEQ ID NO : 148) derived from the coding sequence of SEQ ID NO : 147 shown in Figure 147.

Figure 149 shows a nucleotide sequence (SEQ ID NO : 149) of a native sequence wherein SEQ ID NO : 149 is a clone designated herein as"DNA56869-1545".

Figure 150 shows the amino acid sequence (SEQ ID NO : 150) derived from the coding sequence of SEQ ID NO : 149 shown in Figure 149.

Figure 151 shows a nucleotide sequence (SEQ ID NO : 151) of a native sequence cDNA, wherein SEQ ID NO : 151 is a clone designated herein as"DNA56870-1492".

Figure 152 shows the amino acid sequence (SEQ ID NO : 152) derived from the coding sequence of SEQ ID NO : 151 shown in Figure

Figure 153 shows a nucleotide sequence : 153) of a native sequence wherein SEQ ID NO : 153 is a clone designated herein as"DNA57039-1402".

Figure 154 shows the amino acid sequence (SEQ ID NO : 154) derived from the coding sequence of SEQ ID NO : 153 shown in Figure 153.

Figure 155 shows a nucleotide sequence (SEQ ID NO : 155) of a native sequence cDNA, wherein SEQ ID NO : 155 is a clone designated herein

Figure 156 shows the amino acid sequence (SEQ ID NO : 156) derived from the coding sequence of SEQ ID NO : 155 shown in Figure 155.

Figure 157 shows a nucleotide sequence (SEQ ID NO : 157) of a native sequence wherein SEQ ID NO : 157 is a clone designated herein as"DNA57254-1477".

Figure 158 shows the amino acid sequence (SEQ ID NO : 158) derived from the coding sequence of SEQ ID NO : 157 shown in Figure 157.

Figure 159 shows a nucleotide sequence (SEQ ID NO : 159) of a native sequence wherein SEQ ID NO : 159 is a clone designated herein as"DNA57699-1412".

Figure 160 shows the amino acid sequence (SEQ ID NO : 160) derived from the coding sequence of SEQ ID NO : 159 shown in Figure 159.

Figure 161 shows a nucleotide sequence (SEQ ID NO : 161) of a native sequence wherein SEQ ID NO : 161 is a clone designated herein as"DNA57704-1452".

Figure 162 shows the amino acid sequence (SEQ ID NO : 162) derived from the coding sequence of SEQ ID NO : 161 shown in Figure

Figure 163 shows a nucleotide sequence (SEQ ID NO : 163) of a native sequence cDNA, wherein SEQ ID NO : 163 is a clone designated herein as"DNA57710-1451".

Figure 164 shows the amino acid sequence (SEQ ID NO : 164) derived from the coding sequence of SEQ ID NO : 163 shown in Figure 163.

Figure 165 shows a nucleotide sequence (SEQ ID NO : 165) of a native sequence cDNA, wherein SEQ ID NO : 165 is a clone designated herein as"DNA57827-1493".

Figure 166 shows the amino acid sequence (SEQ ID NO : 166) derived from the coding sequence of SEQ ID NO : 165 shown in Figure 165.

Figure 167 shows a nucleotide sequence (SEQ ID NO : 167) of a native sequence wherein SEQ ID NO : 167 is a clone designated herein as"DNA57844-1410".

Figure 168 shows the amino acid sequence (SEQ ID NO : 168) derived from the coding sequence of SEQ ID NO : 167 shown in Figure 167.

Figure 169 shows a nucleotide sequence (SEQ ID NO : 169) of a native sequence wherein SEQ ID NO : 169 is a clone designated herein as"DNA58723-1588".

Figure 170 shows the amino acid sequence (SEQ ID NO : 170) derived from the coding sequence of SEQ ID NO : 169 shown in Figure 169.

Figure 171 shows a nucleotide sequence (SEQ ID NO : 171) of a native sequence cDNA, wherein SEQ ID NO : 171 is a clone designated herein

Figure 172 shows the amino acid sequence (SEQ ID NO : 172) derived from the coding sequence of SEQ ID NO : 171 shown in Figure 171.

Figure 173 shows a nucleotide sequence (SEQ ID NO : 173) of a native sequence wherein SEQ ID NO : 173 is a clone designated herein as"DNA58730-1607".

Figure 174 shows the amino acid sequence (SEQ ID NO : 174) derived from the coding sequence of SEQ ID NO : 173 shown in Figure 173.

Figure 175 shows a nucleotide sequence (SEQ ID NO : 175) of a native sequence PRO 1481 cDNA, wherein SEQ ID NO : 175 is a clone designated herein

Figure 176 shows the amino acid sequence (SEQ ID NO : 176) derived from the coding sequence of SEQ ID NO : 175 shown in Figure 175.

Figure 177 shows a nucleotide sequence (SEQ ID NO : 177) of a native sequence wherein SEQ ID NO : 177 is a clone designated herein as"DNA58737-1473".

Figure 178 shows the amino acid sequence (SEQ ID NO : 178) derived from the coding sequence of SEQ ID NO : 177 shown in Figure 177.

Figure 179 shows a nucleotide sequence (SEQ ID NO : 179) of a native sequence PRO 1383 cDNA, wherein SEQ ID NO : 179 is a clone designated herein as"DNA58743-1609".

Figure 180 shows the amino acid sequence (SEQ ID NO : 180) derived from the coding sequence of SEQ ID NO : 179 shown in Figure 179.

Figure 181 shows a nucleotide sequence (SEQ ID NO : 181) of a native sequence wherein SEQ ID NO : 181 is a clone designated herein as"DNA58747-1384".

Figure 182 shows the amino acid sequence (SEQ ID NO : 182) derived from the coding sequence of SEQ ID NO : 181 shown in Figure 181.

Figure 183 shows a nucleotide sequence (SEQ ID NO : 183) of a native sequence wherein SEQ ID NO : 183 is a clone designated herein as"DNA58828-1519".

Figure 184 shows the amino acid sequence (SEQ ID NO : 184) derived from the coding sequence of SEQ ID NO : 183 shown in Figure 183.

Figure 185 shows a nucleotide sequence (SEQ ID NO : 185) of a native sequence wherein SEQ ID NO : 185 is a clone designated herein as"DNA58846-1409".

Figure 186 shows the amino acid sequence (SEQ ID NO : 186) derived from the coding sequence of SEQ ID NO : 185 shown in Figure

Figure 187 shows a nucleotide sequence (SEQ ID NO : 187) of a native sequence wherein SEQ ID NO : 187 is a clone designated herein as"DNA58848-1472".

Figure 188 shows the amino acid sequence (SEQ ID NO : 188) derived from the coding sequence of SEQ ID NO : 187 shown in Figure 187.

Figure 189 shows a nucleotide sequence (SEQ ID NO : 189) of a native sequence wherein SEQ ID NO : 189 is a clone designated herein as"DNA58849-1494".

Figure 190 shows the amino acid sequence (SEQ ID NO : 190) derived from the coding sequence of SEQ ID NO : 189 shown in Figure 189.

Figure 191 shows a nucleotide sequence (SEQ ID NO : 191) of a native sequence cDNA, wherein SEQ ID NO : 191 is a clone designated herein

Figure 192 shows the amino acid sequence (SEQ ID NO : 192) derived from the coding sequence of SEQ ID NO : 191 shown in Figure 191.

Figure 193 shows a nucleotide sequence (SEQ ID NO : 193) of a native sequence wherein : 193 is a clone designated herein as"DNA58852-1637".

Figure 194 shows the amino acid sequence (SEQ ID NO : 194) derived from the coding sequence of SEQ ID NO : 193 shown in Figure 193.

Figure 195 shows a nucleotide sequence (SEQ ID NO : 195) of a native sequence wherein SEQ ID NO : 195 is a clone designated herein as"DNA58853-1423".

Figure 196 shows the amino acid sequence (SEQ ID NO : 196) derived from the coding sequence of SEQ ID NO : 195 shown in Figure 195.

Figure 197 shows a nucleotide sequence (SEQ ID NO : 197) of a native sequence PR0994 cDNA, wherein SEQ ID NO : 197 is a clone designated herein as"DNA58855-1422".

Figure 198 shows the amino acid sequence (SEQ ID NO : 198) derived from the coding sequence of SEQ ID NO : 197 shown in Figure 197.

Figure 199 shows a nucleotide sequence (SEQ ID NO : 199) of a native sequence wherein SEQ ID NO : 199 is a clone designated herein as"DNA59211-1450".

Figure 200 shows the amino acid sequence (SEQ ID NO : 200) derived from the coding sequence of SEQ ID NO : 199 shown in Figure 199.

Figure 201 shows a nucleotide sequence : 201) of a native sequence cDNA, wherein SEQ ID NO : 201 is a clone designated herein as"DNA59212-1627".

Figure 202 shows the amino acid sequence (SEQ ID NO : 202) derived from the coding sequence of SEQ ID NO : 201 shown in Figure 201.

Figure 203 shows a nucleotide sequence (SEQ ID NO : 203) of a native sequence cDNA, wherein SEQ ID NO : 203 is a clone designated herein as"DNA59213-1487".

Figure 204 shows the amino acid sequence (SEQ ID NO : 204) derived from the coding sequence of SEQ ID NO : 203 shown in Figure 203.

Figure 205 shows a nucleotide sequence (SEQ ID NO : 205) of a native sequence cDNA, wherein SEQ ID NO : 205 is a clone designated herein as"DNA59219-1613".

Figure 206 shows the amino acid sequence (SEQ ID NO : 206) derived from the coding sequence of SEQ ID NO : 205 shown in Figure 205.

Figure 207 shows a nucleotide sequence (SEQ ID NO : 207) of a native sequence cDNA, wherein SEQ ID NO : 207 is a clone designated herein as"DNA59497-1496".

Figure 208 shows the amino acid sequence (SEQ ID NO : 208) derived from the coding sequence of SEQ ID NO : 207 shown in Figure 207.

Figure 209 shows a nucleotide sequence (SEQ ID NO : 209) of a native sequence cDNA, wherein SEQ ID NO : 209 is a clone designated herein as"DNA59602-1436".

Figure 210 shows the amino acid sequence (SEQ ID NO : 210) derived from the coding sequence of SEQ ID NO : 209 shown in Figure 209.

Figure 211 shows a nucleotide sequence (SEQ ID NO : 211) of a native sequence cDNA, wherein SEQ ID NO : 211 is a clone designated herein as"DNA59603-1419".

Figure 212 shows the amino acid sequence (SEQ ID NO : 212) derived from the coding sequence of SEQ ID NO : 211 shown in Figure 211.

Figure 213 shows a nucleotide sequence (SEQ ID NO : 213) of a native sequence cDNA, wherein SEQ ID NO : 213 is a clone designated herein as"DNA59605-1418".

Figure 214 shows the amino acid sequence (SEQ ID NO : 214) derived from the coding sequence of SEQ ID NO : 213 shown in Figure 213.

Figure 215 shows a nucleotide sequence (SEQ ID NO : 215) of a native sequence cDNA, wherein SEQ ID NO : 215 is a clone designated herein as"DNA59607-1497".

Figure 216 shows the amino acid sequence (SEQ ID NO : 216) derived from the coding sequence of SEQ ID NO : 215 shown in Figure 215.

Figure 217 shows a nucleotide sequence (SEQ ID NO : 217) of a native sequence cDNA, wherein SEQ ID NO : 217 is a clone designated herein as"DNA59610-1556".

Figure 218 shows the amino acid sequence (SEQ ID NO : 218) derived from the coding sequence of SEQ ID NO : 217 shown in Figure 217.

Figure 219 shows a nucleotide sequence (SEQ ID NO : 219) of a native sequence cDNA, wherein SEQ ID NO : 219 is a clone designated herein as"DNA59612-1466".

Figure 220 shows the amino acid sequence (SEQ ID NO : 220) derived from the coding sequence of SEQ ID NO : 219 shown in Figure 219.

Figure 221 shows a nucleotide sequence (SEQ ID NO : 221) of a native sequence cDNA, wherein SEQ ID NO : 221 is a clone designated herein

Figure 222 shows the amino acid sequence (SEQ ID NO : 222) derived from the coding sequence of SEQ ID NO : 221 shown in Figure 221.

Figure 223 shows a nucleotide sequence (SEQ ID NO : 223) of a native sequence cDNA, wherein SEQ ID NO : 223 is a clone designated herein as"DNA59616-1465".

Figure 224 shows the amino acid sequence (SEQ ID NO : 224) derived from the coding sequence of SEQ ID NO : 223 shown in Figure 223.

Figure 225 shows a nucleotide sequence (SEQ ID NO : 225) of a native sequence cDNA, wherein SEQ ID NO : 225 is a clone designated herein as"DNA59619-1464".

Figure 226 shows the amino acid sequence (SEQ ID NO : 226) derived from the coding sequence of SEQ ID NO : 225 shown in Figure 225.

Figure 227 shows a nucleotide sequence (SEQ ID NO : 227) of a native sequence cDNA, wherein SEQ ID NO : 227 is a clone designated herein as"DNA59625-1498".

Figure shows the amino acid sequence (SEQ ID NO : derived from the coding sequence of SEQ ID NO : 227 shown in Figure 227.

Figure 229 shows a nucleotide sequence (SEQ ID NO : 229) of a native sequence cDNA, wherein SEQ ID NO : 229 is a clone designated herein as"DNA59817-1703".

Figure 230 shows the amino acid sequence (SEQ ID NO : 230) derived from the coding sequence of SEQ ID NO : 229 shown in Figure 229.

Figure 231 shows a nucleotide sequence (SEQ ID NO : 231) of a native sequence cDNA, wherein SEQ ID NO : 231 is a clone designated herein

Figure 232 shows the amino acid sequence (SEQ ID NO : 232) derived from the coding sequence of SEQ ID NO : 231 shown in Figure

Figure 233 shows a nucleotide sequence (SEQ ID NO : 233) of a native sequence cDNA, wherein SEQ ID NO : 233 is a clone designated herein

Figure 234 shows the amino acid sequence (SEQ ID NO : 234) derived from the coding sequence of SEQ ID NO : 233 shown in Figure 233.

Figure 235 shows a nucleotide sequence (SEQ ID NO : 235) of a native sequence PR03573 cDNA, wherein SEQ ID NO : 235 is a clone designated herein as"DNA59837-2545".

Figure 236 shows the amino acid sequence (SEQ ID NO : 236) derived from the coding sequence of SEQ ID NO : 235 shown in Figure 235.

Figure 237 shows a nucleotide sequence (SEQ ID NO : 237) of a native sequence PR03566 cDNA, wherein SEQ ID NO : 237 is a clone designated herein as"DNA59844-2542".

Figure 238 shows the amino acid sequence (SEQ ID NO : 238) derived from the coding sequence of SEQ ID NO : 237 shown in Figure 237.

Figure 239 shows a nucleotide sequence (SEQ ID NO : 239) of a native sequence cDNA, wherein SEQ ID NO : 239 is a clone designated herein

Figure 240 shows the amino acid sequence (SEQ ID NO : 240) derived from the coding sequence of SEQ ID NO : 239 shown in Figure 239.

Figure 241 shows a nucleotide sequence (SEQ ID NO : 241) of a native sequence cDNA, wherein SEQ ID NO : 241 is a clone designated herein as"DNA59854-1459".

Figure 242 shows the amino acid sequence (SEQ ID NO : 242) derived from the coding sequence of SEQ ID NO : 241 shown in Figure 241.

Figure 243 shows a nucleotide sequence (SEQ ID NO : 243) of a native sequence wherein SEQ ID NO : 243 is a clone designated herein

Figure 244 shows the amino acid sequence (SEQ ID NO : 244) derived from the coding sequence of SEQ ID NO : 243 shown in Figure 243.

Figure 245 shows a nucleotide sequence (SEQ ID NO : 245) of a native sequence cDNA, wherein SEQ ID NO : 245 is a clone designated herein

Figure 246 shows the amino acid sequence (SEQ ID NO : 246) derived from the coding sequence of SEQ ID NO : 245 shown in Figure 245.

Figure 247 shows a nucleotide sequence (SEQ ID NO : 247) of a native sequence cDNA, wherein SEQ ID NO : 247 is a clone designated herein as"DNA60283-1484".

Figure 248 shows the amino acid sequence (SEQ ID NO : 248) derived from the coding sequence of SEQ ID NO : 247 shown in Figure 247.

Figure 249 shows a nucleotide sequence (SEQ ID NO : 249) of a native sequence cDNA, wherein SEQ ID NO : 249 is a clone designated herein as"DNA60608-1577".

Figure 250 shows the amino acid sequence (SEQ ID NO : 250) derived from the coding sequence of SEQ ID NO : 249 shown in Figure 249.

Figure 251 shows a nucleotide sequence (SEQ ID NO : 251) of a native sequence cDNA, wherein : 251 is a clone designated herein as"DNA60611-1524".

Figure 252 shows the amino acid sequence (SEQ ID NO : 252) derived from the coding sequence of SEQ ID NO : 251 shown in Figure 251.

Figure 253 shows a nucleotide sequence (SEQ ID NO : 253) of a native sequence wherein : 253 is a clone designated herein as"DNA60619-1482".

Figure 254 shows the amino acid sequence (SEQ ID NO : 254) derived from the coding sequence of SEQ ID NO : 253 shown in Figure 253.

Figure 255 shows a nucleotide sequence (SEQ ID NO : 255) of a native sequence cDNA, wherein SEQ ID NO : 255 is a clone designated herein as"DNA60625-1507".

Figure 256 shows the amino acid sequence (SEQ ID NO : 256) derived from the coding sequence of SEQ ID NO : 255 shown in Figure 255.

Figure 257 shows a nucleotide sequence (SEQ ID NO : 257) of a native sequence cDNA, wherein : 257 is a clone designated herein as"DNA60629-1481".

Figure 258 shows the amino acid sequence (SEQ ID NO : 258) derived from the coding sequence of SEQ ID NO : 257 shown in Figure 257.

Figure 259 shows a nucleotide sequence (SEQ ID NO : 259) of a native sequence cDNA, wherein SEQ ID NO : 259 is a clone designated herein as"DNA60740-1615".

Figure 260 shows the amino acid sequence (SEQ ID NO : 260) derived from the coding sequence of SEQ ID NO : 259 shown in Figure 259.

Figure 261 shows a nucleotide sequence (SEQ ID NO : 261) of a native sequence cDNA, wherein SEQ ID NO : 261 is a clone designated herein

Figure 262 shows the amino acid sequence (SEQ ID NO : 262) derived from the coding sequence of SEQ ID NO : 261 shown in Figure 261.

Figure 263 shows a nucleotide sequence (SEQ ID NO : 263) of a native sequence cDNA, wherein SEQ ID NO : 263 is a clone designated herein as"DNA61755-1554".

Figure 264 shows the amino acid sequence : 264) derived from the coding sequence of SEQ ID NO : 263 shown in Figure

Figure 265 shows a nucleotide sequence (SEQ ID NO : 265) of a native sequence cDNA, wherein SEQ ID NO : 265 is a clone designated herein as"DNA62809-1531".

Figure 266 shows the amino acid sequence (SEQ ID NO : 266) derived from the coding sequence of SEQ ID NO : 265 shown in Figure

Figure 267 shows a nucleotide sequence (SEQ ID NO : 267) of a native sequence wherein SEQ ID NO : 267 is a clone designated herein

Figure 268 shows the amino acid sequence (SEQ ID NO : 268) derived from the coding sequence of SEQ ID NO : 267 shown in Figure 267.

Figure 269 shows a nucleotide sequence (SEQ ID NO : 269) of a native sequence PR03572 cDNA, wherein SEQ ID NO : 269 is a clone designated herein as"DNA62813-2544".

Figure 270 shows the amino acid sequence (SEQ ID NO : 270) derived from the coding sequence of SEQ ID NO : 269 shown in Figure 269.

Figure 271 shows a nucleotide sequence (SEQ ID NO : 271) of a native sequence cDNA, wherein SEQ ID NO : 271 is a clone designated herein as"DNA62845-1684".

Figure 272 shows the amino acid sequence (SEQ ID NO : 272) derived from the coding sequence of SEQ ID NO : 271 shown in Figure 271.

Figure 273 shows a nucleotide sequence (SEQ ID NO : 273) of a native sequence cDNA, wherein SEQ ID NO : 273 is a clone designated herein as"DNA64849-1604".

Figure 274 shows the amino acid sequence (SEQ ID NO : 274) derived from the coding sequence of SEQ ID NO : 273 shown in Figure 273.

Figure 275 shows a nucleotide sequence (SEQ ID NO : 275) of a native sequence cDNA, wherein SEQ ID NO : 275 is a clone designated herein as"DNA64852-1589".

Figure 276 shows the amino acid sequence (SEQ ID NO : 276) derived from the coding sequence of SEQ ID NO : 275 shown in Figure 275.

Figure 277 shows a nucleotide sequence (SEQ ID NO : 277) of a native sequence cDNA, wherein SEQ ID NO : 277 is a clone designated herein as"DNA64863-1573".

Figure 278 shows the amino acid sequence (SEQ ID NO : 278) derived from the coding sequence of SEQ ID NO : 277 shown in Figure 277.

Figure 279 shows a nucleotide sequence (SEQ ID NO : 279) of a native sequence cDNA, wherein SEQ ID NO : 279 is a clone designated herein as"DNA64881-1602".

Figure 280 shows the amino acid sequence (SEQ ID NO : 280) derived from the coding sequence of SEQ ID NO : 279 shown in Figure 279.

Figure 281 shows a nucleotide sequence (SEQ ID NO : 281) of a native sequence cDNA, wherein SEQ ID NO : 281 is a clone designated herein as"DNA64902-1667".

Figure 282 shows the amino acid sequence (SEQ ID NO : 282) derived from the coding sequence of SEQ ID NO : shown in Figure

Figure 283 shows a nucleotide sequence (SEQ ID NO : 283) of a native sequence cDNA, wherein SEQ ID NO : 283 is a clone designated herein as"DNA64952-1568".

Figure 284 shows the amino acid sequence (SEQ ID NO : 284) derived from the coding sequence of SEQ ID NO : 283 shown in Figure

Figure 285 shows a nucleotide sequence (SEQ ID NO : 285) of a native sequence cDNA, wherein SEQ ID NO : 285 is a clone designated herein as"DNA65403-1565".

Figure 286 shows the amino acid sequence (SEQ ID NO : 286) derived from the coding sequence of SEQ ID NO : 285 shown in Figure 285.

Figure 287 shows a nucleotide sequence (SEQ ID NO : 287) of a native sequence cDNA, wherein : 287 is a clone designated herein

Figure 288 shows the amino acid sequence (SEQ ID NO : 288) derived from the coding sequence of SEQ ID NO : 287 shown in Figure 287.

Figures 289A-289B show a nucleotide sequence (SEQ ID NO : 289) of a native sequence cDNA, wherein SEQ ID NO : 289 is a clone designated herein as"DNA65423-1595".

Figure 290 shows the amino acid sequence (SEQ ID NO : 290) derived from the coding sequence of SEQ ID NO : 289 shown in Figures 289A-289B.

Figure 291 shows a nucleotide sequence (SEQ ID NO : 291) of a native sequence cDNA, wherein SEQ ID NO : 291 is a clone designated herein as"DNA66304-1546".

Figure 292 shows the amino acid sequence (SEQ ID NO : 292) derived from the coding sequence of SEQ ID NO : 291 shown in Figure 291.

Figure 293 shows a nucleotide sequence (SEQ ID NO : 293) of a native sequence wherein : 293 is a clone designated herein as"DNA66308-1537".

Figure 294 shows the amino acid sequence (SEQ ID NO : 294) derived from the coding sequence of SEQ ID NO : 293 shown in Figure 293.

Figure 295 shows a nucleotide sequence (SEQ ID NO : 295) of a native sequence cDNA, wherein SEQ ID NO : 295 is a clone designated herein as"DNA66511-1563".

Figure 296 shows the amino acid sequence : 296) derived from the coding sequence of SEQ ID NO : 295 shown in Figure 295.

Figure 297 shows a nucleotide sequence : 297) of a native sequence cDNA, wherein SEQ ID NO : 297 is a clone designated herein as"DNA66512-1564".

Figure 298 shows the amino acid sequence (SEQ ID NO : 298) derived from the coding sequence of SEQ ID NO : 297 shown in Figure 297.

Figure 299 shows a nucleotide sequence (SEQ ID NO : 299) of a native sequence cDNA, wherein SEQ ID NO : 299 is a clone designated herein as"DNA66519-1535".

Figure 300 shows the amino acid sequence (SEQ ID NO : 300) derived from the coding sequence of SEQ ID NO : 299 shown in Figure 299.

Figure 301 shows a nucleotide sequence (SEQ ID NO : 301) of a native sequence cDNA, wherein SEQ ID NO : 301 is a clone designated herein as"DNA66521-1583".

Figure 302 shows the amino acid sequence (SEQ ID NO : 302) derived from the coding sequence of SEQ ID NO : 301 shown in Figure 301.

Figure 303 shows a nucleotide sequence (SEQ ID NO : 303) of a native sequence cDNA, wherein SEQ ID NO : 303 is a clone designated herein as"DNA66658-1584".

Figure 304 shows the amino acid sequence (SEQ ID NO : 304) derived from the coding sequence of SEQ ID NO : 303 shown in Figure 303.

Figure 305 shows a nucleotide sequence (SEQ ID NO : 305) of a native sequence cDNA, wherein SEQ ID NO : 305 is a clone designated herein as"DNA66660-1585".

Figure 306 shows the amino acid sequence (SEQ ID NO : 306) derived from the coding sequence of SEQ ID NO : 305 shown in Figure 305.

Figure 307 shows a nucleotide sequence (SEQ ID NO : 307) of a native sequence cDNA, wherein SEQ ID NO : 307 is a clone designated herein as"DNA66669-1597".

Figure shows the amino acid sequence (SEQ ID NO : 308) derived from the coding sequence of SEQ ID NO : 307 shown in Figure 307.

Figure 309 shows a nucleotide sequence (SEQ ID NO : 309) of a native sequence cDNA, wherein SEQ ID NO : 309 is a clone designated herein as"DNA66674-1599".

Figure 310 shows the amino acid sequence (SEQ ID NO : 310) derived from the coding sequence of SEQ ID NO : 309 shown in Figure 309.

Figures 311A-311B show a nucleotide sequence (SEQ ID NO : 311) of a native sequence cDNA, wherein SEQ ID NO : 311 is a clone designated herein as"DNA68836-1656".

Figure 312 shows the amino acid sequence (SEQ ID NO : 312) derived from the coding sequence of SEQ ID NO : 311 shown in Figures

Figure 313 shows a nucleotide sequence (SEQ ID NO : 313) of a native sequence PR03579 cDNA, wherein SEQ ID NO : 313 is a clone designated herein as"DNA68862-2546".

Figure 314 shows the amino acid sequence (SEQ ID NO : 314) derived from the coding sequence of SEQ ID NO : 313 shown in Figure 313.

Figure 315 shows a nucleotide sequence (SEQ ID NO : 315) of a native sequence cDNA, wherein SEQ ID NO : 315 is a clone designated herein

Figure 316 shows the amino acid sequence (SEQ ID NO : 316) derived from the coding sequence of SEQ ID NO : 315 shown in Figure 315.

Figure 317 shows a nucleotide sequence (SEQ ID NO : 317) of a native sequence PRO1385 cDNA, wherein SEQ ID NO : 317 is a clone designated herein as"DNA68869-1610".

Figure 318 shows the amino acid sequence (SEQ ID NO : 318) derived from the coding sequence of SEQ ID NO : 317 shown in Figure 317.

Figure 319 shows a nucleotide sequence (SEQ ID NO : 319) of a native sequence cDNA, wherein SEQ ID NO : 319 is a clone designated herein

Figure 320 shows the amino acid sequence (SEQ ID NO : 320) derived from the coding sequence of SEQ ID NO : 319 shown in Figure 319.

Figure 321 shows a nucleotide sequence (SEQ ID NO : 321) of a native sequence cDNA, wherein SEQ ID NO : 321 is a clone designated herein as"DNA68879-1631".

Figure 322 shows the amino acid sequence (SEQ ID NO : 322) derived from the coding sequence of SEQ ID NO : 321 shown in Figure 321.

Figure 323 shows a nucleotide sequence (SEQ ID NO : 323) of a native sequence cDNA, wherein SEQ ID NO : 323 is a clone designated herein as"DNA68880-1676".

Figure 324 shows the amino acid sequence (SEQ ID NO : 324) derived from the coding sequence of SEQ ID NO : 323 shown in Figure 323.

Figure 325 shows a nucleotide sequence (SEQ ID NO : 325) of a native sequence cDNA, wherein SEQ ID NO : 325 is a clone designated herein as"DNA68882-1677".

Figure 326 shows the amino acid sequence (SEQ ID NO : 326) derived from the coding sequence of SEQ ID NO : 325 shown in Figure 325.

Figure 327 shows a nucleotide sequence (SEQ ID NO : 327) of a native sequence cDNA, wherein SEQ ID NO : 327 is a clone designated herein as"DNA68883-1691".

Figure 328 shows the amino acid sequence (SEQ ID NO : 328) derived from the coding sequence of SEQ ID NO : 327 shown in Figure 327.

Figure 329 shows a nucleotide sequence : 329) of a native sequence cDNA, wherein SEQ ID NO : 329 is a clone designated herein as"DNA68885-1678".

Figure 330 shows the amino acid sequence (SEQ ID NO : 330) derived from the coding sequence of SEQ ID NO : 329 shown in Figure 329.

Figure 331 shows a nucleotide sequence (SEQ ID NO : 331) of a native sequence cDNA, wherein SEQ ID NO : 331 is a clone designated herein as"DNA68886".

Figure 332 shows the amino acid sequence (SEQ ID NO : 332) derived from the coding sequence of SEQ ID NO : 331 shown in Figure 331.

Figure 333 shows a nucleotide sequence (SEQ ID NO : 333) of a native sequence cDNA, wherein SEQ ID NO : 333 is a clone designated herein as"DNA71180-1655".

Figure 334 shows the amino acid sequence (SEQ ID NO : 334) derived from the coding sequence of SEQ ID NO : 333 shown in Figure 333.

Figure 335 shows a nucleotide sequence (SEQ ID NO : 335) of a native sequence wherein SEQ ID NO : 335 is a clone designated herein as"DNA71184-1634".

Figure 336 shows the amino acid sequence (SEQ ID NO : 336) derived from the coding sequence of SEQ ID NO : 335 shown in Figure 335.

Figure 337 shows a nucleotide sequence (SEQ ID NO : 337) of a native sequence cDNA, wherein SEQ ID NO : 337 is a clone designated herein as"DNA71213-1659".

Figure 338 shows the amino acid sequence (SEQ ID NO : 338) derived from the coding sequence of SEQ ID NO : 337 shown in Figure 337.

Figure 339 shows a nucleotide sequence (SEQ ID NO : 339) of a native sequence cDNA, wherein SEQ ID NO : 339 is a clone designated herein as"DNA71234-1651".

Figure 340 shows the amino acid sequence (SEQ ID NO : 340) derived from the coding sequence of SEQ ID NO : 339 shown in Figure 339.

Figure 341 shows a nucleotide sequence (SEQ ID NO : 341) of a native sequence cDNA, wherein SEQ ID NO : 341 is a clone designated herein as"DNA71269-1621".

Figure 342 shows the amino acid sequence (SEQ ID NO : 342) derived from the coding sequence of SEQ ID NO : 341 shown in Figure 341.

Figure 343 shows a nucleotide sequence (SEQ ID NO : 343) of a native sequence cDNA, wherein SEQ ID NO : 343 is a clone designated herein as"DNA71277-1636".

Figure 344 shows the amino acid sequence (SEQ ID NO : 344) derived from the coding sequence of SEQ ID NO : 343 shown in Figure 343.

Figure 345 shows a nucleotide sequence (SEQ ID NO : 345) of a native sequence cDNA, wherein SEQ ID NO : 345 is a clone designated herein as"DNA71286-1687".

Figure 346 shows the amino acid sequence (SEQ ID NO : 346) derived from the coding sequence of SEQ ID NO : 345 shown in Figure 345.

Figure 347 shows a nucleotide sequence : 347) of a native sequence cDNA, wherein SEQ ID NO : 347 is a clone designated herein as"DNA71883-1660".

Figure shows the amino acid sequence (SEQ ID NO : 348) derived from the coding sequence of SEQ ID NO : 347 shown in Figure 347.

Figure 349 shows a nucleotide sequence (SEQ ID NO : 349) of a native sequence cDNA, wherein SEQ ID NO : 349 is a clone designated herein

Figure 350 shows the amino acid sequence (SEQ ID NO : 350) derived from the coding sequence of SEQ ID NO : 349 shown in Figure 349.

Figures 351A-351B show a nucleotide sequence (SEQ ID NO : 351) of a native sequence cDNA, wherein SEQ ID NO : 351 is a clone designated herein as"DNA73492-1671".

Figure 352 shows the amino acid sequence (SEQ ID NO : 352) derived from the coding sequence of SEQ ID NO : 351 shown in Figures 351A-351B.

Figure 353 shows a nucleotide sequence (SEQ ID NO : 353) of a native sequence cDNA, wherein SEQ ID NO : 353 is a clone designated herein as"DNA73730-1679".

Figure 354 shows the amino acid sequence (SEQ ID NO : 354) derived from the coding sequence of SEQ ID NO : 353 shown in Figure 353.

Figure 355 shows a nucleotide sequence (SEQ ID NO : 355) of a native sequence cDNA, wherein SEQ ID NO : 355 is a clone designated herein as"DNA73734-1680".

Figure 356 shows the amino acid sequence (SEQ ID NO : 356) derived from the coding sequence of SEQ ID NO : 355 shown in Figure 355.

Figure 357 shows a nucleotide sequence (SEQ ID NO : 357) of a native sequence cDNA, wherein SEQ ID NO : 357 is a clone designated herein as"DNA73735-1681".

Figure 358 shows the amino acid sequence (SEQ ID NO : 358) derived from the coding sequence of SEQ ID NO : 357 shown in Figure 357.

Figure 359 shows a nucleotide sequence (SEQ ID NO : 359) of a native sequence cDNA, wherein SEQ ID NO : 359 is a clone designated herein as"DNA73742-1662".

Figure 360 shows the amino acid sequence (SEQ ID NO : 360) derived from the coding sequence of SEQ ID NO : 359 shown in Figure 359.

Figure 361 shows a nucleotide sequence (SEQ ID NO : 361) of a native sequence cDNA, wherein SEQ ID NO : 361 is a clone designated herein as"DNA73746-1654".

Figure 362 shows the amino acid sequence (SEQ ID NO : 362) derived from the coding sequence of SEQ ID NO : 361 shown in Figure 361.

Figure 363 shows a nucleotide sequence (SEQ ID NO : 363) of a native sequence cDNA, wherein SEQ ID NO : 363 is a clone designated herein as"DNA73760-1672".

Figure 364 shows the amino acid sequence (SEQ ID NO : 364) derived from the coding sequence of SEQ ID NO : 363 shown in Figure 363.

Figure 365 shows a nucleotide sequence (SEQ ID NO : 365) of a native sequence cDNA, wherein SEQ ID NO : 365 is a clone designated herein as"DNA76393-1664".

Figure 366 shows the amino acid sequence (SEQ ID NO : 366) derived from the coding sequence of SEQ ID NO : 365 shown in Figure 365.

Figure 367 shows a nucleotide sequence (SEQ ID NO : 367) of a native sequence cDNA, wherein SEQ ID NO : 367 is a clone designated herein as"DNA76398-1699".

Figure 368 shows the amino acid sequence (SEQ ID NO : 368) derived from the coding sequence of SEQ ID NO : 367 shown in Figure 367.

Figure 369 shows a nucleotide sequence (SEQ ID NO : 369) of a native sequence cDNA, wherein SEQ ID NO : 369 is a clone designated herein as"DNA76399-1700".

Figure 370 shows the amino acid sequence (SEQ ID NO : 370) derived from the coding sequence of SEQ ID NO : 369 shown in Figure 369.

Figure 371 shows a nucleotide sequence (SEQ ID NO : 371) of a native sequence cDNA, wherein SEQ ID NO : 371 is a clone designated herein as"DNA76522-2500".

Figure 372 shows the amino acid sequence (SEQ ID NO : 372) derived from the coding sequence of SEQ ID NO : 371 shown in Figure 371.

Figure 373 shows a nucleotide sequence (SEQ ID NO : 373) of a native sequence cDNA, wherein SEQ ID NO : 373 is a clone designated herein

Figure 374 shows the amino acid sequence (SEQ ID NO : 374) derived from the coding sequence of SEQ ID NO : 373 shown in Figure 373.

Figure 375 shows a nucleotide sequence (SEQ ID NO : 375) of a native sequence cDNA, wherein SEQ ID NO : 375 is a clone designated herein as"DNA77303-2502".

Figure 376 shows the amino acid sequence (SEQ ID NO : 376) derived from the coding sequence of SEQ ID NO : 375 shown in Figure 375.

Figure 377 shows a nucleotide sequence (SEQ ID NO : 377) of a native sequence cDNA, wherein SEQ ID NO : 377 is a clone designated herein as"DNA77626-1705".

Figure shows the amino acid sequence (SEQ ID NO : 378) derived from the coding sequence of SEQ ID NO : 377 shown in Figure 377.

Figure 379 shows a nucleotide sequence (SEQ ID NO : 379) of a native sequence cDNA, wherein SEQ ID NO : 379 is a clone designated herein as"DNA77648-1688".

Figure 380 shows the amino acid sequence (SEQ ID NO : 380) derived from the coding sequence of SEQ ID NO : 379 shown in Figure 379.

Figure 381 shows a nucleotide sequence (SEQ ID NO : 381) of a native sequence cDNA, wherein SEQ ID NO : 381 is a clone designated herein as"DNA81754-2532".

Figure 382 shows the amino acid sequence (SEQ ID NO : 382) derived from the coding sequence of SEQ ID NO : 381 shown in Figure 381.

Figure 383 shows a nucleotide sequence (SEQ ID NO : 383) of a native sequence cDNA, wherein SEQ ID NO : 383 is a clone designated herein as"DNA81757-2512".

Figure 384 shows the amino acid sequence (SEQ ID NO : 384) derived from the coding sequence of SEQ ID NO : 383 shown in Figure 383.

Figure 385 shows a nucleotide sequence (SEQ ID NO : 385) of a native sequence cDNA, wherein SEQ ID NO : 385 is a clone designated herein as"DNA82302-2529".

Figure 386 shows the amino acid sequence (SEQ ID NO : 386) derived from the coding sequence of SEQ ID NO : 385 shown in Figure 385.

Figure 387 shows a nucleotide sequence (SEQ ID NO : 387) of a native sequence cDNA, wherein SEQ ID NO : 387 is a clone designated herein as"DNA82340-2530".

Figure 388 shows the amino acid sequence (SEQ ID NO : 388) derived from the coding sequence of SEQ ID NO : 387 shown in Figure 387.

Figure 389 shows a nucleotide sequence (SEQ ID NO : 389) of a native sequence PR02630 cDNA, wherein SEQ ID NO : 389 is a clone designated herein as"DNA83551".

Figure 390 shows the amino acid sequence (SEQ ID NO : 390) derived from the coding sequence of SEQ ID NO : 389 shown in Figure

Figure 391 shows a nucleotide sequence (SEQ ID NO : 391) of a native sequence PR03443 cDNA, wherein SEQ ID NO : 391 is a clone designated herein as"DNA87991-2540".

Figure 392 shows the amino acid sequence (SEQ ID NO : 392) derived from the coding sequence of SEQ ID NO : 391 shown in Figure 391.

Figure 393 shows a nucleotide sequence (SEQ ID NO : 393) of a native sequence PR03301 cDNA, wherein SEQ ID NO : 393 is a clone designated herein as"DNA88002".

Figure 394 shows the amino acid sequence (SEQ ID NO : 394) derived from the coding sequence of SEQ ID NO : 393 shown in Figure 393.

Figure 395 shows a nucleotide sequence (SEQ ID NO : 395) of a native sequence PR03442 cDNA, wherein SEQ ID NO : 395 is a clone designated herein as"DNA92238-2539".

Figure 396 shows the amino acid sequence (SEQ ID NO : 396) derived from the coding sequence of SEQ ID NO : 395 shown in Figure 395.

Figure 397 shows a nucleotide sequence (SEQ ID NO : 397) of a native sequence PR04978 cDNA, wherein SEQ ID NO : 397 is a clone designated herein as"DNA95930".

Figure 398 shows the amino acid sequence (SEQ ID NO : 398) derived from the coding sequence of SEQ ID NO : 397 shown in Figure 397.

Figure 399 shows a nucleotide sequence (SEQ ID NO : 399) of a native sequence PR05801 cDNA, wherein SEQ ID NO : 399 is a clone designated herein

Figure 400 shows the amino acid sequence (SEQ ID NO : 400) derived from the coding sequence of SEQ ID NO : 399 shown in Figure 399.

Figure 401 shows a nucleotide sequence (SEQ ID NO : 401) of a native sequence cDNA, wherein : 401 is a clone designated herein as"DNA23336-2861".

Figure 402 shows the amino acid sequence (SEQ ID NO : 402) derived from the coding sequence of SEQ ID NO : 401 shown in Figure 401.

Figure 403 shows a nucleotide sequence : 403) of a native sequence PR0203 cDNA, wherein SEQ ID NO : 403 is a clone designated herein as"DNA30862-1396".

Figure 404 shows the amino acid sequence (SEQ ID NO : 404) derived from the coding sequence of SEQ ID NO : 403 shown in Figure 403.

Figure 405 shows a nucleotide sequence : 405) of a native sequence PR0204 cDNA, wherein SEQ ID NO : 405 is a clone designated herein as"DNA30871-1157".

Figure 406 shows the amino acid sequence (SEQ ID NO : 406) derived from the coding sequence of SEQ ID NO : 405 shown in Figure 405.

Figure 407 shows a nucleotide sequence (SEQ ID NO : 407) sequence PR0210 cDNA, wherein SEQ ID NO : 407 is a clone designated herein as"DNA32279-1131".

Figure 408 shows the amino acid sequence (SEQ ID NO : 408) derived from the coding sequence of SEQ ID NO : 407 shown in Figure 407.

Figure 409 shows a nucleotide sequence : 409) of a native sequence PR0223 cDNA, wherein SEQ ID NO : 409 is a clone designated herein

Figure 410 shows the amino acid sequence (SEQ ID NO : 410) derived from the coding sequence of SEQ ID NO : 409 shown in Figure 409.

Figure 411 shows a nucleotide sequence (SEQ ID NO : 411) of a native sequence PR0247 cDNA, wherein SEQ ID NO : 411 is a clone designated herein as"DNA35673-1201".

Figure 412 shows the amino acid sequence (SEQ ID NO : 412) derived from the coding sequence of SEQ ID NO : 411 shown in Figure 411.

Figure 413 shows a nucleotide sequence (SEQ ID NO : 413) of a native sequence PR0358 cDNA, wherein SEQ ID NO : 413 is a clone designated herein as"DNA47361-1154-2".

Figure 414 shows the amino acid sequence (SEQ ID NO : 414) derived from the coding sequence of SEQ ID NO : 413 shown in Figure 413.

Figure 415 shows a nucleotide sequence (SEQ ID NO : 415) of a native sequence PR0724 cDNA, wherein SEQ ID NO : 415 is a clone designated herein as"DNA49631-1328".

Figure 416 shows the amino acid sequence (SEQ ID NO : 416) derived from the coding sequence of SEQ ID NO : 415 shown in Figure 415.

Figure 417 shows a nucleotide sequence (SEQ ID NO : 417) wherein SEQ ID NO : 417 is a clone designated herein as"DNA52594-1270".

Figure 418 shows the amino acid sequence (SEQ ID NO : 418) derived from the coding sequence of SEQ ID NO : 417 shown in Figure 417.

Figure 419 shows a nucleotide sequence (SEQ ID NO : 419) of a native sequence PR0740 cDNA, wherein SEQ ID NO : 419 is a clone designated herein as"DNA55800-1263".

Figure 420 shows the amino acid sequence (SEQ ID NO : 420) derived from the coding sequence of SEQ ID NO : 419 shown in Figure 419.

Figure 421 shows a nucleotide sequence (SEQ ID NO : 421) of a native sequence cDNA, wherein SEQ ID NO : 421 is a clone designated herein as"DNA56531-1648".

Figure 422 shows the amino acid sequence (SEQ ID NO : 422) derived from the coding sequence of SEQ ID NO : 421 shown in Figure 421.

Figure 423 shows a nucleotide sequence (SEQ ID NO : 423) of a native sequence wherein SEQ ID NO : 423 is a clone designated herein as"DNA56965-1356".

Figure 424 shows the amino acid sequence (SEQ ID NO : 424) derived from the coding sequence of SEQ ID NO : 423 shown in Figure 423.

Figure 425 shows a nucleotide sequence (SEQ ID NO : 425) of a native sequence cDNA, wherein SEQ ID NO : 425 is a clone designated herein as"DNA57037-1444".

Figure 426 shows the amino acid sequence (SEQ ID NO : 426) derived from the coding sequence of SEQ ID NO : 425 shown in Figure 425.

Figure 427 shows a nucleotide sequence (SEQ ID NO : 427) of a native sequence PRO819 cDNA, wherein SEQ ID NO : 427 is a clone designated herein as"DNA57695-1340".

Figure shows the amino acid sequence (SEQ ID NO : 428) derived from the coding sequence of SEQ ID NO : 427 shown in Figure 427.

Figure 429 shows a nucleotide sequence : 429) of a native sequence wherein SEQ ID NO : 429 is a clone designated herein

Figure 430 shows the amino acid sequence (SEQ ID NO : 430) derived from the coding sequence of SEQ ID NO : 429 shown in Figure 429.

Figure 431 shows a nucleotide sequence (SEQ ID NO : 431) of a native sequence cDNA, wherein SEQ ID NO : 431 is a clone designated herein as"DNA57841-1522".

Figure 432 shows the amino acid sequence (SEQ ID NO : 432) derived from the coding sequence of SEQ ID NO : 431 shown in Figure

Figure 433 shows sequence (SEQ ID NO : 433) of a native sequence PR0887 cDNA, wherein SEQ ID NO : 433 is a clone designated herein as"DNA58130".

Figure 434 shows the amino acid sequence (SEQ ID NO : 434) derived from the coding sequence of SEQ ID NO : 433 shown in Figure 433.

Figure 435 shows a nucleotide sequence (SEQ ID NO : 435) of a native sequence cDNA, wherein SEQ ID NO : 435 is a clone designated herein as"DNA58847-1383".

Figure 436 shows the amino acid sequence (SEQ ID NO : 436) derived from the coding sequence of SEQ ID NO : 435 shown in Figure 435.

Figure 437 shows a nucleotide sequence (SEQ ID NO : 437) of a native sequence cDNA, wherein SEQ ID NO : 437 is a clone designated herein as"DNA59493-1420".

Figure 438 shows the amino acid sequence (SEQ ID NO : 438) derived from the coding sequence of SEQ ID NO : 437 shown in Figure 437.

Figure 439 shows a nucleotide sequence (SEQ ID NO : 439) of a native sequence cDNA, wherein SEQ ID NO : 439 is a clone designated herein as"DNA59586-1520".

Figure 440 shows the amino acid sequence (SEQ ID NO : 440) derived from the coding sequence of SEQ ID NO : 439 shown in Figure 439.

Figure 441 shows a nucleotide sequence (SEQ ID NO : 441) of a native sequence PR04334 cDNA, wherein SEQ ID NO : 441 is a clone designated herein as"DNA59608-2577".

Figure 442 shows the amino acid sequence (SEQ ID NO : 442) derived from the coding sequence of SEQ ID NO : 441 shown in Figure 441.

Figure 443 shows a nucleotide sequence (SEQ ID NO : 443) of a native sequence cDNA, wherein SEQ ID NO : 443 is a clone designated herein as"DNA59849-1504".

Figure 444 shows the amino acid sequence (SEQ ID NO : 444) derived from the coding sequence of SEQ ID NO : 443 shown in Figure 443.

Figure 445 shows a nucleotide sequence (SEQ ID NO : 445) of a native sequence wherein SEQ ID NO : 445 is a clone designated herein as"DNA60292-1506".

Figure 446 shows the amino acid sequence (SEQ ID NO : 446) derived from the coding sequence of SEQ ID NO : 445 shown in Figure 445.

Figure 447 shows a nucleotide sequence (SEQ ID NO : 447) of a native sequence cDNA, wherein SEQ ID NO : 447 is a clone designated herein as"DNA62377-1381-1".

Figure 448 shows the amino acid sequence (SEQ ID NO : 448) derived from the coding sequence of SEQ ID NO : 447 shown in Figure 447.

Figure 449 shows a nucleotide sequence (SEQ ID NO : 449) of a native sequence cDNA, wherein SEQ ID NO : 449 is a clone designated herein as"DNA62880-1513".

Figure 450 shows the amino acid sequence (SEQ ID NO : 450) derived from the coding sequence of SEQ ID NO : 449 shown in Figure 449.

Figure 451 shows a nucleotide sequence (SEQ ID NO : of a native sequence cDNA, wherein SEQ ID NO : 451 is a clone designated herein as"DNA66672-1586".

Figure 452 shows the amino acid sequence (SEQ ID NO : 452) derived from the coding sequence of SEQ ID NO : 451 shown in Figure 451.

Figure 453 shows a nucleotide sequence (SEQ ID NO : 453) of a native sequence cDNA, wherein SEQ ID NO : 453 is a clone designated herein as"DNA67962-1649".

Figure 454 shows the amino acid sequence (SEQ ID NO : 454) derived from the coding sequence of SEQ ID NO : 453 shown in Figure 453.

Figure 455 shows a nucleotide sequence (SEQ ID NO : 455) of a native sequence cDNA, wherein : 455 is a clone designated herein as"DNA69555-2867".

Figure 456 shows the amino acid sequence (SEQ ID NO : 456) derived from the coding sequence of SEQ ID NO : 455 shown in Figure 455.

Figure 457 shows a nucleotide sequence (SEQ ID NO : 457) of a native sequence PR09782 cDNA, wherein SEQ ID NO : 457 is a clone designated herein as"DNA71162-2764".

Figure 458 shows the amino acid sequence (SEQ ID NO : 458) derived from the coding sequence of SEQ ID NO : 457 shown in Figure 457.

Figure 459 shows a nucleotide sequence (SEQ ID NO : 459) of a native sequence cDNA, wherein : 459 is a clone designated herein as"DNA71290-1630".

Figure 460 shows the amino acid sequence (SEQ ID NO : 460) derived from the coding sequence of SEQ ID NO : 459 shown in Figure 459.

Figure 461 shows a nucleotide sequence (SEQ ID NO : 461) of a native sequence cDNA, wherein SEQ ID NO : 461 is a clone designated herein as"DNA76401-1683".

Figure 462 shows the amino acid sequence (SEQ ID NO : 462) derived from the coding sequence of SEQ ID NO : 461 shown in Figure 461.

Figure 463 shows a nucleotide sequence (SEQ ID NO : 463) of a native sequence cDNA, wherein : 463 is a clone designated herein as"DNA76541-1675".

Figure 464 shows the amino acid sequence (SEQ ID NO : 464) derived from the coding sequence of SEQ ID NO : 463 shown in Figure 463.

Figure 465 shows a nucleotide sequence (SEQ ID NO : 465) of a native sequence cDNA, wherein SEQ ID NO : 465 is a clone designated herein as"DNA76788-2526".

Figure 466 shows the amino acid sequence (SEQ ID NO : 466) derived from the coding sequence of SEQ ID NO : 465 shown in Figure 465.

Figure 467 shows a nucleotide sequence (SEQ ID NO : 467) of a native sequence cDNA, wherein SEQ ID NO : 467 is a clone designated herein as"DNA77623-2524".

Figure 468 shows the amino acid sequence (SEQ ID NO : 468) derived from the coding sequence of SEQ ID NO : 467 shown in Figure 467.

Figure 469 shows a nucleotide sequence (SEQ ID NO : 469) of a native sequence cDNA, wherein SEQ ID NO : 469 is a clone designated herein as"DNA80136-2503".

Figure 470 shows the amino acid sequence (SEQ ID NO : 470) derived from the coding sequence of SEQ ID NO : 469 shown in Figure 469.

Figure 471 shows a nucleotide sequence (SEQ ID NO : 471) of a native sequence PR06003 cDNA, wherein SEQ ID NO : 471 is a clone designated herein as"DNA83568-2692".

Figure 472 shows the amino acid sequence (SEQ ID NO : 472) derived from the coding sequence of SEQ ID NO : 471 shown in Figure 471.

Figure 473 shows a nucleotide sequence (SEQ ID NO : 473) of a native sequence PR04333 cDNA, wherein SEQ ID NO : 473 is a clone designated herein as"DNA84210-2576".

Figure 474 shows the amino acid sequence (SEQ ID NO : 474) derived from the coding sequence of SEQ ID NO : 473 shown in Figure 473.

Figure 475 shows a nucleotide sequence (SEQ ID NO : 475) of a native sequence PR04356 cDNA, wherein SEQ ID NO : 475 is a clone designated herein as"DNA86576-2595".

Figure 476 shows the amino acid sequence (SEQ ID NO : 476) derived from the coding sequence of SEQ ID NO : 475 shown in Figure 475.

Figure 477 shows a nucleotide sequence (SEQ ID NO : 477) of a native sequence PR04352 cDNA, wherein SEQ ID NO : 477 is a clone designated herein as"DNA87976-2593".

Figure 478 shows the amino acid sequence (SEQ ID NO : 478) derived from the coding sequence of SEQ ID NO : 477 shown in Figure 477.

Figure 479 shows a nucleotide sequence (SEQ ID NO : 479) of a native sequence PR04354 cDNA, wherein SEQ ID NO : 479 is a clone designated herein as"DNA92256-2596".

Figure 480 shows the amino acid sequence (SEQ ID NO : 480) derived from the coding sequence of SEQ ID NO : 479 shown in Figure 479.

Figure 481 shows a nucleotide sequence (SEQ ID NO : 481) of a native sequence PR04369 cDNA, wherein SEQ ID NO : 481 is a clone designated herein as"DNA92289-2598".

Figure 482 shows the amino acid sequence (SEQ ID NO : 482) derived from the coding sequence of SEQ ID NO : 481 shown in Figure 481.

Figure 483 shows a nucleotide sequence (SEQ ID NO : 483) of a native sequence PR06030 cDNA, wherein SEQ ID NO : 483 is a clone designated herein as"DNA96850-2705".

Figure 484 shows the amino acid sequence (SEQ ID NO : 484) derived from the coding sequence of SEQ ID NO : 483 shown in Figure 483.

Figure 485 shows a nucleotide sequence (SEQ ID NO : 485) of a native sequence PR04433 cDNA, wherein SEQ ID NO : 485 is a clone designated herein as"DNA96855-2629".

Figure 486 shows the amino acid sequence (SEQ ID NO : 486) derived from the coding sequence of SEQ ID NO : 485 shown in Figure 485.

Figure 487 shows a nucleotide sequence (SEQ ID NO : 487) of a native sequence PR04424 cDNA, wherein SEQ ID NO : 487 is a clone designated herein as"DNA96857-2636".

Figure 488 shows the amino acid sequence (SEQ ID NO : 488) derived from the coding sequence of SEQ ID NO : 487 shown in Figure 487.

Figure 489 shows a nucleotide sequence (SEQ ID NO : 489) of a native sequence PR06017 cDNA, wherein SEQ ID NO : 489 is a clone designated herein

Figure 490 shows the amino acid sequence (SEQ ID NO : 490) derived from the coding sequence of SEQ ID NO : 489 shown in Figure 489.

Figure 491 shows a nucleotide sequence (SEQ ID NO : 491) of a native sequence cDNA, wherein SEQ ID NO : 491 is a clone designated herein as"DNA96861-2844".

Figure 492 shows the amino acid sequence (SEQ ID NO : 492) derived from the coding sequence of SEQ ID NO : 491 shown in Figure 491.

Figure 493 shows a nucleotide sequence (SEQ ID NO : 493) of a native sequence PR06015 cDNA, wherein SEQ ID NO : 493 is a clone designated herein

Figure 494 shows the amino acid sequence (SEQ ID NO : 494) derived from the coding sequence of SEQ ID NO : 493 shown in Figure 493.

Figure 495 shows a nucleotide sequence (SEQ ID NO : 495) of a native sequence PR05779 cDNA, wherein SEQ ID NO : 495 is a clone designated herein as"DNA96870-2676".

Figure 496 shows the amino acid sequence (SEQ ID NO : 496) derived from the coding sequence of SEQ ID NO : 495 shown in Figure 495.

Figure 497 shows a nucleotide sequence (SEQ ID NO : 497) of a native sequence PR05776 cDNA, wherein SEQ ID NO : 497 is a clone designated herein

Figure 498 shows the amino acid sequence (SEQ ID NO : 498) derived from the coding sequence of SEQ ID NO : 497 shown in Figure 497.

Figure 499 shows a nucleotide sequence (SEQ ID NO : 499) of a native sequence PR04430 cDNA, wherein SEQ ID NO : is a clone designated herein as"DNA96878-2626".

Figure 500 shows the amino acid sequence (SEQ ID NO : 500) derived from the coding sequence of SEQ ID NO : 499 shown in Figure 499.

Figure 501 shows a nucleotide sequence (SEQ ID NO : 501) of a native sequence PR04421 cDNA, wherein SEQ ID NO : 501 is a clone designated herein as"DNA96879-2619".

Figure 502 shows the amino acid sequence (SEQ ID NO : 502) derived from the coding sequence of SEQ ID NO : 501 shown in Figure 501.

Figure 503 shows a nucleotide sequence (SEQ ID NO : 503) of a native sequence PR04499 cDNA, wherein SEQ ID NO : 503 is a clone designated herein

Figure 504 shows the amino acid sequence (SEQ ID NO : 504) derived from the coding sequence of SEQ ID NO : 503 shown in Figure 503.

Figure 505 shows a nucleotide sequence (SEQ ID NO : 505) of a native sequence PR04423 cDNA, . wherein SEQ ID NO : 505 is a clone designated herein as"DNA96893-2621".

Figure 506 shows the amino acid sequence (SEQ ID NO : 506) derived from the coding sequence of SEQ ID NO : 505 shown in Figure 505.

Figure 507 shows a nucleotide sequence (SEQ ID NO : 507) of a native sequence PR05998 cDNA, wherein SEQ ID NO : 507 is a clone designated herein as"DNA96897-2688".

Figure 508 shows the amino acid sequence (SEQ ID NO : 508) derived from the coding sequence of SEQ ID NO : 507 shown in Figure 507.

Figure 509 shows a nucleotide sequence (SEQ ID NO : 509) of a native sequence PR04501 cDNA, wherein SEQ ID NO : 509 is a clone designated herein as"DNA98564-2643".

Figure 510 shows the amino acid sequence (SEQ ID NO : 510) derived from the coding sequence of SEQ ID NO : 509 shown in Figure 509.

Figure 511 shows a nucleotide sequence (SEQ ID NO : 511) of a native sequence PR06240 cDNA, wherein SEQ ID NO : 511 is a clone designated herein as"DNA107443-2718".

Figure 512 shows the amino acid sequence (SEQ ID NO : 512) derived from the coding sequence of SEQ ID NO : 511 shown in Figure 511.

Figure 513 shows a nucleotide sequence (SEQ ID NO : 513) of a native sequence PR06245 cDNA, wherein SEQ ID NO : 513 is a clone designated herein as"DNA107786-2723".

Figure 514 shows the amino acid sequence (SEQ ID NO : 514) derived from the coding sequence of SEQ ID NO : 513 shown in Figure 513.

Figure 515 shows a nucleotide sequence (SEQ ID NO : 515) of a native sequence PR06175 cDNA, wherein SEQ ID NO : 515 is a clone designated herein as"DNA108682-2712".

Figure 516 shows the amino acid sequence (SEQ ID NO : 516) derived from the coding sequence of SEQ ID NO : 515 shown in Figure 515.

Figure 517 shows a nucleotide sequence (SEQ ID NO : 517) of a native sequence PR09742 cDNA, wherein SEQ ID NO : 517 is a clone designated herein

Figure shows the amino acid sequence (SEQ ID NO : 518) derived from the coding sequence of SEQ ID NO : 517 shown in Figure 517.

Figure 519 shows a nucleotide sequence (SEQ ID NO : 519) of a native sequence PR07179 cDNA, wherein SEQ ID NO : 519 is a clone designated herein as"DNA108701-2749".

Figure 520 shows the amino acid sequence (SEQ ID NO : 520) derived from the coding sequence of SEQ ID NO : 519 shown in Figure 519.

Figure 521 shows a nucleotide sequence (SEQ ID NO : 521) of a native sequence PR06239 cDNA, wherein SEQ ID NO : 521 is a clone designated herein as"DNA108720-2717".

Figure 522 shows the amino acid sequence (SEQ ID NO : 522) derived from the coding sequence of SEQ ID NO : 521 shown in Figure 521.

Figure 523 shows a nucleotide sequence (SEQ ID NO : 523) of a native sequence PR06493 cDNA, wherein SEQ ID NO : 523 is a clone designated herein

Figure 524 shows the amino acid sequence (SEQ ID NO : 524) derived from the coding sequence of SEQ ID NO : 523 shown in Figure 523.

Figures 525A-525B show a nucleotide sequence (SEQ ID NO : 525) of a native sequence PR09741 cDNA, wherein SEQ ID NO : 525 is a clone designated herein as"DNA108728-2760".

Figure 526 shows the amino acid sequence (SEQ ID NO : 526) derived from the coding sequence of SEQ ID NO : 525 shown in Figures 525A-525B.

Figure 527 shows a nucleotide sequence (SEQ ID NO : 527) of a native sequence PR09822 cDNA, wherein SEQ ID NO : 527 is a clone designated herein as"DNA108738-2767".

Figure 528 shows the amino acid sequence (SEQ ID NO : 528) derived from the coding sequence of SEQ ID NO : 527 shown in Figure 527.

Figure 529 shows a nucleotide sequence (SEQ ID NO : 529) of a native sequence PR06244 cDNA, wherein SEQ ID NO : 529 is a clone designated herein as"DNA108743-2722".

Figure 530 shows the amino acid sequence (SEQ ID NO : 530) derived from the coding sequence of SEQ ID NO : 529 shown in Figure 529.

Figure 531 shows a nucleotide sequence (SEQ ID NO : 531) of a native sequence PR09740 cDNA, wherein SEQ ID NO : 531 is a clone designated herein as"DNA108758-2759".

Figure 532 shows the amino acid sequence (SEQ ID NO : 532) derived from the coding sequence of SEQ ID NO : 531 shown in Figure 531.

Figure 533 shows a nucleotide sequence (SEQ ID NO : 533) of a native sequence PR09739 cDNA, wherein SEQ ID NO : 533 is a clone designated herein as"DNA108765-2758".

Figure 534 shows the amino acid sequence (SEQ ID NO : 534) derived from the coding sequence of SEQ ID NO : 533 shown in Figure 533.

Figure 535 shows a nucleotide sequence (SEQ ID NO : 535) of a native sequence PR07177 cDNA, wherein SEQ ID NO : 535 is a clone designated herein as"DNA108783-2747".

Figure 536 shows the amino acid sequence (SEQ ID NO : 536) derived from the coding sequence of SEQ ID NO : 535 shown in Figure 535.

Figure 537 shows a nucleotide sequence (SEQ ID NO : 537) of a native sequence PR07178 cDNA, wherein SEQ ID NO : 537 is a clone designated herein

Figure 538 shows the amino acid sequence : 538) derived from the coding sequence of SEQ ID NO : 537 shown in Figure 537.

Figure 539 shows a nucleotide sequence (SEQ ID NO : 539) of a native sequence PR06246 cDNA, wherein SEQ ID NO : 539 is a clone designated herein as"DNA108806-2724".

Figure 540 shows the amino acid sequence (SEQ ID NO : 540) derived from the coding sequence of SEQ ID NO : 539 shown in Figure 539.

Figure 541 shows a nucleotide sequence (SEQ ID NO : 541) of a native sequence PR06241 cDNA, wherein SEQ ID NO : 541 is a clone designated herein as"DNA108936-2719".

Figure 542 shows the amino acid sequence (SEQ ID NO : 542) derived from the coding sequence of SEQ ID NO : 541 shown in Figure 541.

Figure 543 shows a nucleotide sequence (SEQ ID NO : 543) of a native sequence PR09835 cDNA, wherein SEQ ID NO : 543 is a clone designated herein as"DNA119510-2771".

Figure 544 shows the amino acid sequence (SEQ ID NO : 544) derived from the coding sequence of SEQ ID NO : 543 shown in Figure 543.

Figure 545 shows a nucleotide sequence (SEQ ID NO : 545) of a native sequence PR09857 cDNA, wherein SEQ ID NO : 545 is a clone designated herein

Figure 546 shows the amino acid sequence (SEQ ID NO : 546) derived from the coding sequence of SEQ ID NO : 545 shown in Figure 545.

Figure 547 shows a nucleotide sequence (SEQ ID NO : 547) of a native sequence PR07436 cDNA, wherein SEQ ID NO : 547 is a clone designated herein as"DNA119535-2756".

Figure 548 shows the amino acid sequence (SEQ ID NO : 548) derived from the coding sequence of SEQ ID NO : 547 shown in Figure 547.

Figure 549 shows a nucleotide sequence (SEQ ID NO : 549) of a native sequence PR09856 cDNA, wherein SEQ ID NO : 549 is a clone designated herein as"DNA119537-2777".

Figure 550 shows the amino acid sequence (SEQ ID NO : 550) derived from the coding sequence of SEQ ID NO : 549 shown in Figure 549.

Figure 551 shows a nucleotide sequence (SEQ ID NO : 551) of a native sequence cDNA, wherein SEQ ID NO : 551 is a clone designated herein

Figure 552 shows the amino acid sequence (SEQ ID NO : 552) derived from the coding sequence of SEQ ID NO : 551 shown in Figure 551.

Figure 553 shows a nucleotide sequence (SEQ ID NO : 553) of a native sequence PR09859 cDNA, wherein SEQ ID NO : 553 is a clone designated herein as"DNA125170-2780".

Figure 554 shows the amino acid sequence (SEQ ID NO : 554) derived from the coding sequence of SEQ ID NO : 553 shown in Figure 553.

Figure 555 shows a nucleotide sequence (SEQ ID NO : 555) of a native sequence cDNA, wherein SEQ ID NO : 555 is a clone designated herein as"DNA129594-2841".

Figure 556 shows the amino acid sequence (SEQ ID NO : 556) derived from the coding sequence of SEQ ID NO : 555 shown in Figure 555.

Figure 557 shows a nucleotide sequence (SEQ ID NO : 557) of a native sequence cDNA, wherein SEQ ID NO : 557 is a clone designated herein

Figure 558 shows the amino acid sequence (SEQ ID NO : 558) derived from the coding sequence of SEQ ID NO : 557 shown in Figure 557.

Figure 559 shows a nucleotide sequence (SEQ ID NO : 559) of a native sequence PR09833 cDNA, wherein SEQ ID NO : 559 is a clone designated herein as"DNA130809-2769".

Figure 560 shows the amino acid sequence (SEQ ID NO : 560) derived from the coding sequence of SEQ ID NO : 559 shown in Figure 559.

Figure 561 shows a nucleotide sequence (SEQ ID NO : 561) of a native sequence cDNA, wherein SEQ ID NO : 561 is a clone designated herein as"DNA131639-2874".

Figure 562 shows the amino acid sequence (SEQ ID NO : 562) derived from the coding sequence of SEQ ID NO : shown in Figure 561.

Figure 563 shows a nucleotide sequence (SEQ ID NO : 563) of a native sequence wherein SEQ ID NO : 563 is a clone designated herein as"DNA131649-2855".

Figure 564 shows the amino acid sequence (SEQ ID NO : 564) derived from the coding sequence of SEQ ID NO : 563 shown in Figure 563.

Figure 565 shows a nucleotide sequence (SEQ ID NO : 565) of a native sequence cDNA, wherein SEQ ID NO : 565 is a clone designated herein as"DNA131652-2876".

Figure 566 shows the amino acid sequence (SEQ ID NO : 566) derived from the coding sequence of SEQ ID NO : 565 shown in Figure 565.

Figure 567 shows a nucleotide sequence (SEQ ID NO : 567) of a native sequence cDNA, wherein SEQ ID NO : 567 is a clone designated herein as"DNA131658-2875".

Figure 568 shows the amino acid sequence (SEQ ID NO : 568) derived from the coding sequence of SEQ ID NO : 567 shown in Figure 567.

Figure 569 shows a nucleotide sequence (SEQ ID NO : 569) of a native sequence PR09834 cDNA, wherein SEQ ID NO : 569 is a clone designated herein as"DNA132162-2770".

Figure 570 shows the amino acid sequence (SEQ ID NO : 570) derived from the coding sequence of SEQ ID NO : 569 shown in Figure 569.

Figure 571 shows a nucleotide sequence (SEQ ID NO : 571) of a native sequence PR09744 cDNA, wherein SEQ ID NO : 571 is a clone designated herein as"DNA136110-2763".

Figure 572 shows the amino acid sequence (SEQ ID NO : derived from the coding sequence of SEQ ID NO : 571 shown in Figure 571.

Figure 573 shows a nucleotide sequence (SEQ ID NO : 573) of a native sequence cDNA, wherein SEQ ID NO : 573 is a clone designated herein as"DNA139592-2866".

Figure 574 shows the amino acid sequence (SEQ ID NO : 574) derived from the coding sequence of SEQ ID NO : 573 shown in Figure 573.

Figure 575 shows a nucleotide sequence (SEQ ID NO : 575) of a native sequence cDNA, wherein SEQ ID NO : 575 is a clone designated herein as"DNA139608-2856".

Figure 576 shows the amino acid sequence (SEQ ID NO : 576) derived from the coding sequence of SEQ ID NO : 575 shown in Figure 575.

Figure 577 shows a nucleotide sequence (SEQ ID NO : 577) of a native sequence cDNA, wherein SEQ ID NO : 577 is a clone designated herein as"DNA143292-2848".

Figure 578 shows the amino acid sequence (SEQ ID NO : 578) derived from the coding sequence of SEQ ID NO : 577 shown in Figure 577.

Figure 579 shows a nucleotide sequence (SEQ ID NO : 579) of a native sequence cDNA, wherein SEQ ID NO : 579 is a clone designated herein as"DNA144844-2843".

Figure 580 shows the amino acid sequence (SEQ ID NO : 580) derived from the coding sequence of SEQ ID NO : 579 shown in Figure 579.

Figure 581 shows a nucleotide sequence (SEQ ID NO : 581) of a native sequence cDNA, wherein SEQ ID NO : 581 is a clone designated herein

Figure 582 shows the amino acid sequence (SEQ ID NO : 582) derived from the coding sequence of SEQ ID NO : 581 shown in Figure 581.

Figure 583 shows a nucleotide sequence (SEQ ID NO : 583) of a native sequence cDNA, wherein SEQ ID NO : 583 is a clone designated herein as"DNA145841-2868".

Figure 584 shows the amino acid sequence (SEQ ID NO : 584) derived from the coding sequence of SEQ ID NO : 583 shown in Figure 583.

Figure 585 shows a nucleotide sequence (SEQ ID NO : 585) of a native sequence cDNA, wherein SEQ ID NO : 585 is a clone designated herein as"DNA148004-2882".

Figure 586 shows the amino acid sequence (SEQ ID NO : 586) derived from the coding sequence of SEQ ID NO : 585 shown in Figure 585.

Figure 587 shows a nucleotide sequence (SEQ ID NO : 587) of a native sequence cDNA, wherein SEQ ID NO : 587 is a clone designated herein as"DNA149893-2873".

Figure 588 shows the amino acid sequence (SEQ ID NO : 588) derived from the coding sequence of SEQ ID NO : 587 shown in Figure 587.

Figure 589 shows a nucleotide sequence (SEQ ID NO : 589) of a native sequence cDNA, wherein SEQ ID NO : 589 is a clone designated herein as"DNA149930-2884".

Figure 590 shows the amino acid sequence : 590) derived from the coding sequence of SEQ ID NO : 589 shown in Figure 589.

Figure 591 shows a nucleotide sequence (SEQ ID NO : 591) of a native sequence PR020088 cDNA, wherein SEQ ID NO : 591 is a clone designated herein

Figure 592 shows the amino acid sequence (SEQ ID NO : 592) derived from the coding sequence of SEQ ID NO : 591 shown in Figure 591.

Figure 593 shows a nucleotide sequence (SEQ ID NO : 593) of a native sequence cDNA, wherein SEQ ID NO : 593 is a clone designated herein as"DNA150163-2842".

Figure 594 shows the amino acid sequence (SEQ ID NO : 594) derived from the coding sequence of SEQ ID NO : 593 shown in Figure 593.

Figure 595 shows a nucleotide sequence (SEQ ID NO : 595) of a native sequence PR020025 cDNA, wherein SEQ ID NO : 595 is a clone designated herein as"DNA153579-2894".

Figure 596 shows the amino acid sequence (SEQ ID NO : 596) derived from the coding sequence of SEQ ID NO : 595 shown in Figure 595.

Figure 597 shows a nucleotide sequence (SEQ ID NO : 597) of a native sequence PR020040 cDNA, wherein SEQ ID NO : 597 is a clone designated herein as"DNA164625-2890".

Figure 598 shows the amino acid sequence (SEQ ID NO : 598) derived from the coding sequence of SEQ ID NO : 597 shown in Figure 597.

Figure 599 shows a nucleotide sequence (SEQ ID NO : 599) of a native sequence PR0791 cDNA, wherein SEQ ID NO : 599 is a clone designated herein as"DNA57838-1337".

Figure 600 shows the amino acid sequence (SEQ ID NO : 600) derived from the coding sequence of SEQ ID NO : 599 shown in Figure 599.

Figure 601 shows a nucleotide sequence (SEQ ID NO : 601) of a native sequence cDNA, wherein SEQ ID NO : 601 is a clone designated herein as"DNA59777-1480".

Figure 602 shows the amino acid sequence (SEQ ID NO : 602) derived from the coding sequence of SEQ ID NO : 601 shown in Figure 601.

Figure 603 shows a nucleotide sequence (SEQ ID NO : 603) of a native sequence cDNA, wherein SEQ ID NO : 603 is a clone designated herein as"DNA66675-1587".

Figure 604 shows the amino acid sequence (SEQ ID NO : 604) derived from the coding sequence of SEQ ID NO : 603 shown in Figure 603.

Figure 605 shows a nucleotide sequence (SEQ ID NO : 605) of a native sequence cDNA, wherein SEQ ID NO : 605 is a clone designated herein as"DNA76532-1702".

Figure 606 shows the amino acid sequence (SEQ ID NO : 606) derived from the coding sequence of SEQ ID NO : 605 shown in Figure 605.

Figure 607 shows a nucleotide sequence (SEQ ID NO : 607) of a native sequence PR06029 cDNA, wherein SEQ ID NO : 607 is a clone designated herein as"DNA105849-2704".

Figure 608 shows the amino acid sequence (SEQ ID NO : 608) derived from the coding sequence of SEQ ID NO : 607 shown in Figure 607.

Figure 609 shows a nucleotide sequence (SEQ ID NO : 609) of a native sequence wherein SEQ ID NO : 609 is a clone designated herein as"DNA83500-2506".

Figure 610 shows the amino acid sequence (SEQ ID NO : 610) derived from the coding sequence of SEQ ID NO : 609 shown in Figure 609.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS I. Definitions The terms"PRO polypeptide"and"PRO"as used herein and when immediately followed by a numerical designation refer to various polypeptides, wherein the complete designation (i. e., refers to specific polypeptide sequences as described herein. The terms"PRO/number the term"number"is provided as an actual numerical designation as used herein encompass native sequence polypeptides and polypeptide variants (which are further defined herein). The PRO polypeptides described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods. The term"PRO polypeptide"refers to each individual PRO/number polypeptide disclosed herein. All disclosures in this specification which refer to the"PRO polypeptide"refer to each of the polypeptides individually as well as jointly. For example, descriptions of the preparation of, purification of, derivation of, formation of antibodies to or against, administration of, compositions containing, treatment of a disease with, etc., pertain to each polypeptide of the invention individually. The term"PRO polypeptide"also includes variants of the PRO/number polypeptides disclosed herein.

A"native sequence PRO polypeptide"comprises a polypeptide having the same amino acid sequence as the corresponding PRO polypeptide derived from nature. Such native sequence PRO polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term"native sequence PRO polypeptide" specifically encompasses naturally-occurring truncated or secreted forms of the specific PRO polypeptide (e. g., an extracellular domain sequence), naturally-occurring variant forms (e. g., alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide. In various embodiments of the invention, the native sequence PRO polypeptides disclosed herein are mature or full-length native sequence polypeptides comprising the full-length amino acids sequences shown in the accompanying figures. Start and stop codons are shown in bold font and underlined in the

figures. However, while the PRO polypeptide disclosed in the accompanying figures are shown to begin with methionine residues designated herein as amino acid position 1 in the figures, it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the PRO polypeptides.

The PRO polypeptide"extracellular domain"or"ECD"refers to a form of the PRO polypeptide which is essentially free of the transmembrane and cytoplasmic domains. Ordinarily, a PRO polypeptide will have less than 1 % of such transmembrane and/or cytoplasmic domains and preferably, will have less than 0. 5 % of such domains. It will be understood that any transmembrane domains identified for the PRO polypeptides of the present invention are identified pursuant to criteria routinely employed in the art for identifying that type of hydrophobic domain. The exact boundaries of a transmembrane domain may vary but most likely by no more than about 5 amino acids at either end of the domain as initially identified herein. Optionally, therefore, an extracellular domain of a PRO polypeptide may contain from about 5 or fewer amino acids on either side of the transmembrane domain/extracellular domain boundary as identified in the Examples or specification and such polypeptides, with or without the associated signal peptide, and nucleic acid encoding them, are comtemplated by the present invention.

The approximate location of the"signal peptides"of the various PRO polypeptides disclosed herein are shown in the present specification and/or the accompanying figures. It is noted, however, that the C-terminal boundary of a signal peptide may vary, but most likely by no more than about 5 amino acids on either side of the signal peptide C-terminal boundary as initially identified herein, wherein the C-terminal boundary of the signal peptide may be identified pursuant to criteria routinely employed in the art for identifying that type of amino acid sequence element (e. g., Nielsen et al., Prot. Eng. 10 : 1-6 (1997) and von Heinje et al., Nucl. Acids. Res.

14 : 4683-4690 (1986)). Moreover, it is also recognized that, in some cases, cleavage of a signal sequence from a secreted polypeptide is not entirely uniform, resulting in more than one secreted species. These mature polypeptides, where the signal peptide is cleaved within no more than about 5 amino acids on either side of the C-terminal boundary of the signal peptide as identified herein, and the polynucleotides encoding them, are contemplated by the present invention.

"PRO polypeptide variant"means an active PRO polypeptide as defined above or below having at least about 80% amino acid sequence identity with a full-length native sequence PRO polypeptide sequence as disclosed herein, a PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Such PRO polypeptide variants include, for instance, PRO polypeptides wherein one or more amino acid residues are added, or deleted, at the N-or C-terminus of the full- length native amino acid sequence. Ordinarily, a PRO polypeptide variant will have at least about 80% amino acid sequence identity, alternatively at least about 81 % amino acid sequence identity, alternatively at least about 82% amino acid sequence identity, alternatively at least about amino acid sequence identity, alternatively at least about amino acid sequence identity, alternatively at least about amino acid sequence identity, alternatively at least about 86% amino acid sequence identity, alternatively at least about 87% amino acid sequence identity, alternatively at least about amino acid sequence identity, alternatively at least about amino acid sequence identity, alternatively at least about 90% amino acid sequence identity, alternatively at least about amino acid sequence identity, alternatively at least about amino acid sequence identity, alternatively at least about 93% amino acid sequence identity, alternatively at least about 94% amino acid sequence identity, alternatively at least about acid sequence identity, alternatively at least about 96 % amino acid sequence identity, alternatively at least about 97 % amino acid sequence identity, alternatively at least about acid sequence identity and alternatively at least about 99% amino acid sequence identity to a full-length native sequence PRO polypeptide sequence as disclosed herein, a PRO

polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, PRO variant polypeptides are at least about 10 amino acids in length, alternatively at least about 20 amino acids in length, alternatively at least about 30 amino acids in length, alternatively at least about 40 amino acids in length, alternatively at least about 50 amino acids in length, alternatively at least about 60 amino acids in length, alternatively at least about 70 amino acids in length, alternatively at least about 80 amino acids in length, alternatively at least about 90 amino acids in length, alternatively at least about 100 amino acids in length, alternatively at least about 150 amino acids in length, alternatively at least about 200 amino acids in length, alternatively at least about 300 amino acids in length, or more.

"Percent (%) amino acid sequence identity"with respect to the PRO polypeptide sequences identified herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific PRO polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U. S. Copyright Office, Washington D. C., 20559, where it is registered under U. S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4. 0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows : 100 times the fraction X/Y where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B.

It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. As examples of % amino acid sequence identity calculations using this method, Tables 2 and 3 demonstrate how to calculate the % amino acid sequence identity of the amino acid sequence designated "Comparison Protein"to the amino acid sequence designated"PRO", wherein"PRO"represents the amino acid sequence of a hypothetical PRO polypeptide of Protein"represents the amino acid sequence of a polypeptide against which the"PRO"polypeptide of interest is being compared, and"X,"Y"and"Z"each represent different hypothetical amino acid residues.

Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program. However, % amino acid sequence identity values may also be obtained as described below by using the WU-

BLAST-2 computer program (Altschul et al., Methods in 266 : 460-480 (1996)). Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, i. e., the adjustable parameters, are set with the following values : overlap span = 1, overlap fraction = 0. 125, word threshold (T) = 11, and scoring matrix = BLOSUM62. When WU-BLAST-2 is employed, a % amino acid sequence identity value is determined by dividing (a) the number of matching identical amino acid residues between the amino acid sequence of the PRO polypeptide of interest having a sequence derived from the native PRO polypeptide and the comparison amino acid sequence of interest (i. e., the sequence against which the PRO polypeptide of interest is being compared which may be a PRO variant polypeptide) as determined by WU-BLAST-2 by (b) the total number of amino acid residues of the PRO polypeptide of interest. For example, in the statement"a polypeptide comprising an the amino acid sequence A which has or having at least amino acid sequence identity to the amino acid sequence B", the amino acid sequence A is the comparison amino acid sequence of interest and the amino acid sequence B is the amino acid sequence of the PRO polypeptide of interest.

Percent amino acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et Nucleic Acids Res. 25 : 3389-3402 (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from http ://www. nlm. nih. gov or otherwise obtained from the National Institute of Health, Bethesda, MD. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask strand = all, expected occurrences = 10, minimum low complexity length = multi-pass e-value 01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

In situations where NCBI-BLAST2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows : 100 times the fraction X/Y where X is the number of amino acid residues scored as identical matches by the sequence alignment program NCBI-BLAST2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A.

"PRO variant polynucleotide"or"PRO variant nucleic acid sequence"means a nucleic acid molecule which encodes an active PRO polypeptide as defined below and which has at least about 80% nucleic acid sequence identity with a nucleotide acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Ordinarily, a PRO variant polynucleotide will have at least about nucleic acid sequence identity, alternatively at least about 81 % nucleic acid sequence identity, alternatively at least about 82 % nucleic acid sequence identity, alternatively at least about 83% nucleic acid sequence identity, alternatively at least about 84% nucleic acid sequence identity, alternatively at least about 85% nucleic acid sequence identity, alternatively at least about 86% nucleic acid sequence identity, alternatively at least about 87 % nucleic acid sequence identity, alternatively at least about 88 nucleic acid sequence identity, alternatively at least about 89 % nucleic acid sequence identity, alternatively at least about 90% nucleic acid sequence identity, alternatively at least about nucleic acid sequence identity, alternatively at least about nucleic acid sequence identity, alternatively at least about nucleic acid sequence identity, alternatively at least about nucleic acid sequence identity, alternatively at least about 95 % nucleic acid sequence identity, alternatively at least about 96 % nucleic acid sequence identity, alternatively at least about 97% nucleic acid sequence identity, alternatively at least about 98% nucleic acid sequence identity and alternatively at least about 99 % nucleic acid sequence identity with a

nucleic acid sequence encoding a full-length native sequence PRO polypeptide sequence as disclosed herein, a full-length native sequence PRO polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a PRO polypeptide, with or without the signal sequence, as disclosed herein or any other fragment of a full-length PRO polypeptide sequence as disclosed herein. Variants do not encompass the native nucleotide sequence.

Ordinarily, PRO variant polynucleotides are at least about 30 nucleotides in length, alternatively at least about 60 nucleotides in length, alternatively at least about 90 nucleotides in length, alternatively at least about 120 nucleotides in length, alternatively at least about 150 nucleotides in length, alternatively at least about 180 nucleotides in length, alternatively at least about 210 nucleotides in length, alternatively at least about 240 nucleotides in length, alternatively at least about 270 nucleotides in length, alternatively at least about 300 nucleotides in length, alternatively at least about 450 nucleotides in length, alternatively at least about 600 nucleotides in length, alternatively at least about 900 nucleotides in length, or more.

"Percent (%) nucleic acid sequence identity"with respect to PRO-encoding nucleic acid sequences identified herein is defined as the percentage of nucleotides in a candidate sequence that are identical with the nucleotides in the PRO nucleic acid sequence of interest, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. For purposes herein, however, % nucleic acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U. S.

Copyright Office, Washington D. C., 20559, where it is registered under U. S. Copyright Registration No.

TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4. 0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for nucleic acid sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows : 100 times the fraction W/Z where W is the number of nucleotides scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C.

As examples of % nucleic acid sequence identity calculations, Tables 4 and 5, demonstrate how to calculate the % nucleic acid sequence identity of the nucleic acid sequence DNA"to the nucleic acid sequence designated"PRO-DNA", wherein"PRO-DNA"represents a hypothetical PRO-encoding nucleic acid sequence of interest,"Comparison DNA"represents the nucleotide sequence of a nucleic acid molecule against which the"PRO-DNA"nucleic acid molecule of interest is being compared, and"N","L"and"V"each represent different hypothetical nucleotides.

Unless specifically stated otherwise, all % nucleic acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program. However, % nucleic acid sequence identity values may also be obtained as described below by using the WU-BLAST-2 computer program (Altschul et Methods in 266 : 460-480 (1996)). Most of the WU-BLAST-2 search parameters are set to the default values. Those not set to default values, i. e., the adjustable parameters, are set with the following values : overlap span = 1, overlap fraction = 0. 125, word threshold (T) = 11, and scoring matrix = BLOSUM62. When WU-BLAST-2 is employed, a % nucleic acid sequence identity value is determined by dividing (a) the number of matching identical nucleotides between the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest having a sequence derived from the native sequence PRO polypeptide-encoding nucleic acid and the comparison nucleic acid molecule of interest (i. e., the sequence against which the PRO polypeptide-encoding nucleic acid molecule of interest is being compared which may be a variant PRO polynucleotide) as determined by WU-BLAST-2 by (b) the total number of nucleotides of the PRO polypeptide-encoding nucleic acid molecule of interest. For example, in the statement"an isolated nucleic acid molecule comprising a nucleic acid sequence A which has or having at least 80% nucleic acid sequence identity to the nucleic acid sequence B", the nucleic acid sequence A is the comparison nucleic acid molecule of interest and the nucleic acid sequence B is the nucleic acid sequence of the PRO polypeptide-encoding nucleic acid molecule of interest.

Percent nucleic acid sequence identity may also be determined using the sequence comparison program NCBI-BLAST2 (Altschul et Nucleic Acids Res. 25 : (1997)). The NCBI-BLAST2 sequence comparison program may be downloaded from http ://www. ncbi. nlm. nih. gov or otherwise obtained from the National Institute of Health, Bethesda, MD. NCBI-BLAST2 uses several search parameters, wherein all of those search parameters are set to default values including, for example, unmask = yes, strand = all, expected occurrences = 10, minimum low complexity length = multi-pass e-value = 0. 01, constant for multi-pass = 25, dropoff for final gapped alignment = 25 and scoring matrix = BLOSUM62.

In situations where is employed for sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows : 100 times the fraction W/Z where W is the number of nucleotides scored as identical matches by the sequence alignment program NCBI- BLAST2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C.

In other embodiments, PRO variant polynucleotides are nucleic acid molecules that encode an active PRO polypeptide and which are capable of hybridizing, preferably under stringent hybridization and wash conditions, to nucleotide sequences encoding a full-length PRO polypeptide as disclosed herein. PRO variant polypeptides may be those that are encoded by a PRO variant polynucleotide.

"Isolated,"when used to describe the various polypeptides disclosed herein, means polypeptide that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the polypeptide will be purified (1) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or, preferably, silver stain. Isolated polypeptide includes polypeptide situ within recombinant cells, since at least one component of the PRO polypeptide natural environment

will not be present. Ordinarily, however, isolated polypeptide will be prepared by at least one purification step.

An"isolated"PRO polypeptide-encoding nucleic acid or other polypeptide-encoding nucleic acid is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the natural source of the polypeptide-encoding nucleic acid. An isolated polypeptide-encoding nucleic acid molecule is other than in the form or setting in which it is found in nature.

Isolated polypeptide-encoding nucleic acid molecules therefore are distinguished from the specific polypeptide- encoding nucleic acid molecule as it exists in natural cells. However, an isolated polypeptide-encoding nucleic acid molecule includes polypeptide-encoding nucleic acid molecules contained in cells that ordinarily express the polypeptide where, for example, the nucleic acid molecule is in a chromosomal location different from that of natural cells.

The sequences"refers to DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize promoters, polyadenylation signals, and enhancers.

Nucleic acid is"operably linked"when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide ; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence ; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally,"operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

The term"antibody"is used in the broadest sense and specifically covers, for example, single anti-PRO monoclonal antibodies (including agonist, antagonist, and neutralizing antibodies), anti-PRO antibody compositions with polyepitopic specificity, single chain anti-PRO antibodies, and fragments of anti-PRO antibodies (see below).

The term"monoclonal antibody"as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i. e., the individual antibodies comprising the population are identical except for possible naturally-occurring mutations that may be present in minor amounts.

"Stringency"of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration.

In general, longer probes require higher temperatures for proper annealing, while shorter probes need lower temperatures. Hybridization generally depends on the ability of denatured DNA to reanneal when complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature which can be used.

As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional details and explanation of stringency of hybridization reactions, see Ausubel et Current Protocols in Molecular Biology, Wiley Interscience Publishers, (1995).

"Stringent conditions"or"high stringency conditions", as defined herein, may be identified by those that : (1) employ low ionic strength and high temperature for washing, for example 0. 015 M sodium chloride/0. 0015 M sodium citrate/0. 1 % sodium dodecyl sulfate at 50°C ; (2) employ during hybridization a denaturing agent, such as formamide, for example, (v/v) formamide with 0. 1% bovine serum albumin/0. Ficoll/0. 1% sodium phosphate buffer at pH 6. 5 with 750 mM sodium chloride, 75 mM sodium citrate at ; or (3) employ 50% formamide, 5 x SSC (0. 75 M NaCl, 0. 075 M sodium citrate), 50 mM sodium phosphate (pH 6. 8), 0. sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 0. 1 % SDS, and 10% dextran sulfate at 42°C, with washes at in 0. 2 x SSC (sodium chloride/sodium citrate) and formamide at followed by a high-stringency wash consisting of 0. 1 x SSC containing

"Moderately stringent conditions"may be identified as described by Sambrook et al., Molecular Cloning : A Laboratory Manual, New York : Cold Spring Harbor Press, 1989, and include the use of washing solution and hybridization conditions (e. g., temperature, ionic strength and % SDS) less stringent that those described above.

An example of moderately stringent conditions is overnight incubation at in a solution comprising : 20% formamide, 5 x SSC (150 mM 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7. 6), 5 x Denhardt's solution, 10% dextran sulfate, and 20 mg/ml denatured sheared salmon sperm DNA, followed by washing the filters in 1 x SSC at about The skilled artisan will recognize how to adjust the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

The term"epitope tagged"when used herein refers to a chimeric polypeptide comprising a PRO polypeptide fused to a"tag polypeptide". The tag polypeptide has enough residues to provide an epitope against which an antibody can be made, yet is short enough such that it does not interfere with activity of the polypeptide to which it is fused. The tag polypeptide preferably also is fairly unique so that the antibody does not substantially cross-react with other epitopes. Suitable tag polypeptides generally have at least six amino acid residues and usually between about 8 and 50 amino acid residues (preferably, between about 10 and 20 amino acid residues).

As used herein, the term"immunoadhesin"designates antibody-like molecules which combine the binding specificity of a heterologous protein (an"adhesin") with the effector functions of immunoglobulin constant domains. Structurally, the comprise a fusion of an amino acid sequence with the desired binding specificity which is other than the antigen recognition and binding site of an antibody (i. e., is"heterologous"), and an immunoglobulin constant domain sequence. The adhesin part of an immunoadhesin molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any immunoglobulin, such as IgG-2, IgG-3, or IgG-4 subtypes, IgA (including and IgA-2), IgE, IgD or IgM.

"Active"or"activity"for the purposes herein refers to form (s) of a PRO polypeptide which retain a biological and/or an immunological activity of native or naturally-occurring PRO, wherein"biological"activity refers to a biological function (either inhibitory or caused by a native or naturally-occurring PRO other than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring PRO and refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring

PRO.

The term"antagonist"is used in the broadest sense, and includes any molecule that partially or fully blocks, inhibits, or neutralizes a biological activity of a native PRO polypeptide disclosed herein. In a similar manner, the term"agonist"is used in the broadest sense and includes any molecule that mimics a biological activity of a native PRO polypeptide disclosed herein. Suitable agonist or antagonist molecules specifically include agonist or antagonist antibodies or antibody fragments, fragments or amino acid sequence variants of native PRO polypeptides, peptides, antisense oligonucleotides, small organic molecules, etc. Methods for identifying agonists or antagonists of a PRO polypeptide may comprise contacting a PRO polypeptide with a candidate agonist or antagonist molecule and measuring a detectable change in one or more biological activities normally associated with the PRO polypeptide.

"Treatment"refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) the targeted pathologic condition or disorder. Those in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented.

"Chronic"administration refers to administration of the agent (s) in a continuous mode as opposed to an acute mode, so as to maintain the initial therapeutic effect (activity) for an extended period of time."Intermittent" administration is treatment that is not consecutively done without interruption, but rather is cyclic in nature.

purposes of treatment refers to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats, rabbits, etc. Preferably, the mammal is human.

combination with"one or more further therapeutic agents includes simultaneous (concurrent) and consecutive administration in any order.

"Carriers"as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers which are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids ; antioxidants including ascorbic acid ; low molecular weight (less than about 10 residues) polypeptide ; proteins, such as serum albumin, gelatin, or immunoglobulins ; hydrophilic polymers such as polyvinylpyrrolidone ; amino acids such as glycine, glutamine, asparagine, arginine or lysine ; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins ; chelating agents such as EDTA ; sugar alcohols such as mannitol or sorbitol ; salt-forming counterions such as sodium ; and/or nonionic surfactants such as TWEEN, polyethylene glycol (PEG), and

"Antibody fragments"comprise a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F (ab') 2, and Fv fragments ; diabodies ; linear antibodies (Zapata et Protein Eng. 8 (10) : 1057-1062 [1995]) ; single-chain antibody molecules ; and multispecific antibodies formed from antibody fragments.

Papain digestion of antibodies produces two identical antigen-binding fragments, called"Fab"fragments, each with a single antigen-binding site, and a residual"Fc"fragment, a designation reflecting the ability to crystallize readily. Pepsin treatment yields an F (ab') fragment that has two antigen-combining sites and is still capable of cross-linking antigen.

"Fv"is the minimum antibody fragment which contains a complete antigen-recognition and-binding site.

This region consists of a dimer of one heavy-and one light-chain variable domain in tight, non-covalent association. It is in this configuration that the three CDRs of each variable domain interact to define an antigen- binding site on the surface of the dimer. Collectively, the six CDRs confer antigen-binding specificity to the antibody. However, even a single variable domain (or half of an comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

The Fab fragment also contains the constant domain of the light chain and the first constant domain of the heavy chain. Fab fragments differ from Fab'fragments by the addition of a few residues at the carboxy terminus of the heavy chain domain including one or more cysteines from the antibody hinge region.

Fab'-SH is the designation herein for Fab'in which the cysteine residue (s) of the constant domains bear a free thiol group. F (ab') 2 antibody fragments originally were produced as pairs of Fab'fragments which have hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The"light chains"of antibodies (immunoglobulins) from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant domains.

Depending on the amino acid sequence of the constant domain of their heavy chains, immunoglobulins can be assigned to different classes. There are five major classes of immunoglobulins : IgA, IgD, IgE, IgG, and IgM, and several of these may be further divided into subclasses (isotypes), e. g., IgG2, IgG3, IgG4, IgA, and IgA2.

"Single-chain Fv"or"sFv"antibody fragments comprise the and VL domains of antibody, wherein these domains are present in a single polypeptide chain. Preferably, the polypeptide further comprises a polypeptide linker between the VH and VL domains which enables the sFv to form the desired structure for antigen binding. For a review of sFv, see in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenburg and Moore Springer-Verlag, New York, pp. 269-315 (1994).

The term"diabodies"refers to small antibody fragments with two antigen-binding sites, which fragments comprise a heavy-chain variable domain connected to a light-chain variable domain in the same polypeptide chain using a linker that is too short to allow pairing between the two domains on the same chain, the domains are forced to pair with the complementary domains of another chain and create two antigen-binding sites. Diabodies are described more fully in, for example, EP 404, 097 ; WO 93/11161 ; and Hollinger et al., Proc. Natl. Acad. Sci. USA, 90 : 6444-6448 (1993).

An"isolated"antibody is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified (1) to greater than 95 % by weight of antibody as determined by the Lowry method, and most preferably more than 99 % by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody in situ within recombinant cells since at least one component of the antibody's natural environment will not be present.

Ordinarily, however, isolated antibody will be prepared by at least one purification step.

An antibody that"specifically binds to"or is"specific for"a particular polypeptide or an epitope on a particular polypeptide is one that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope.

The word"label"when used herein refers to a detectable compound or composition which is conjugated directly or indirectly to the antibody so as to generate a"labeled"antibody. The label may be detectable by itself (e. g. radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition which is detectable.

phase"is meant a non-aqueous matrix to which the antibody of the present invention can adhere. Examples of solid phases encompassed herein include those formed partially or entirely of glass (e. g., controlled pore glass), polysaccharides (e. g., agarose), polyacrylamides, polystyrene, polyvinyl alcohol and silicones. In certain embodiments, depending on the context, the solid phase can comprise the well of an assay plate ; in others it is a purification column (e. g., an affinity chromatography column). This term also includes a discontinuous solid phase of discrete particles, such as those described in U. S. Patent No. 4, 275, 149.

A"liposome"is a small vesicle composed of various types of lipids, phospholipids surfactant which is useful for delivery of a drug (such as a PRO polypeptide or antibody thereto) to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes.

A"small molecule"is defined herein to have a molecular weight below about 500 Daltons.

An"effective amount"of a polypeptide disclosed herein or an agonist or antagonist thereof is an amount sufficient to carry out a specifically stated purpose. An"effective amount"may be determined empirically and in a routine manner, in relation to the stated purpose.

Table 1 * C-C increased from 12 to 15 Z is average of EQ B is average of ND * match with stop ; stop-stop = 0 ; J (joker) match = value of a match with a stop int day [26] [26] { A */ {2, 0,-2, 0, 0,-4, 1,-1,-1, 0,-1,-2,-1, 0,_M, 1, 0,-2, 1, 1, 0, 0,-6, 0,-3, 0}, /* B 3, 2,-5, 0, 1,-2, 0, 0,-3,-2, 2,_M,-1, 1, 0, 0, 0, 0,-2,-5, 0,-3, 1}, /* */ {-2,-4, 15,-5,-5,-4,-3,-3,-2, 0,-2, 0,-2,-8, 0, /* D */ {0, 3,-5, 4, 3,-6, 1, 1,-2, 0, 0,-4,-3, 2,-1, 0, 0, 0,-2,-7, 0,-4, 2}, /* E 3, 4,-5, 0, 1,-2, 0, 0,-3,-2, 0, 0, 0,-2,-7, 0,-4, 3}, /* F */ {-4,-5,-4,-6,-5, 9,-5,-2, 1, 0,-5, 2, 0,-1, 0, 0, G */ {1, 0,-3, 1, 0,-5, 5,-2,-3, 0, 1, 0, 0,-5, 0}, /* H 1, 1,-2,-2, 6,-2, 0, 0,-2,-2, 0, 3, 0,-2,-3, 0, 0, 2}, /* 1,-3,-2, 5, 0,-2, 2, 2,-2, 0, 0, 4,-5, /*J*/ {0,0,0,0,0,0,0,0,0,0,0,0,0,0,_M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0}, K 0,-5, 0, 0,-5,-2, 0,-2, 0, 5,-3, 0, 1, 1, 3, 0, 0, 0,-2,-3, 0,-4, 0}, /* L 6, 0, 2,-2, 0,-3,-2, 2, 0, 0, 4, /* N 2, 1,-4, 0, 2,-2, 0, 1,-3,-2, 2, 1, 0, 1, 0, 0,-2,-4, 0,-2, /*O*/ {_M,_M, M, M, M, M, M, M, M, M, M, M, M, M, M, M, M, M, M,_M, M, M, M}, /* 1,-1,-3,-1,-1,-5,-1, 0,-2, 0,-1,-3,-2,-1,_M,6,0,0,1,0,0,-6,0,-5,0}, /*Q*/ {0,1,-5, 2, 2,-5,-1, 3,-2, 0, 0, 4, 0,-4, /* R 0, 0, 0, 0, 1, 6, 0,-2, 2, 0,-4, /*S*/ {1,0, 0, 0, 0,-3, 0,-3,-2, 0, 2, 1, 0}, /* T */ {1, 0,-2, 0, 0,-3, 0,-1, 0, 0, 0, 0,-1,-1, 1, 3, 0, 0,-5, 0,-3, 0}, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0}, /* 4, 2, 0, 0, 4,-6, /* W 0,-7,-3,-5, 2,-2,-5, 0,-6, /* */ {-3-3, 0,-4,-4, 7,-5, 0,-1, 0,-2, 0, 0, 1,-5, 0, 0, 0, 3, 0, 0, 0, 0,-2,-6, 0,-4, 4} Table 1 #include < stdio.h > #include #define MAXJMP 16/* max jumps in a diag MAXGAP 24/* don't continue to penalize gaps larger than this #define JMPS #define MX 4/* save if there's at least bases since last jmp #define DMAT 3/* value of matching bases #define DMIS penalty for mismatched bases #define DINSO 8/* penalty for a gap DINS1 penalty per base #define PINSO 8/* penalty for a gap PINS1 4/* penalty per residue struct jmp { short n [MAXJMP] ;/* size of jmp (neg for dely) unsigned short x [MAXJMP] ;/* base no. of jmp in seq x struct diag { int score ;/* score at last jmp long offset ;/* offset of block short ijmp ;/* current jmp

index struct jmp struct path { int spc ;/* number of leading spaces short n [JMPS] ;/* size of jmp (gap) */ int x [JMPS] ;/* loc of jmp (last elem before gap) char output file name char *namex ;/* seq names : getseqs () */ char *prog prog name for err msgs char *seqx [2] ;/* seqs : int dmax ;/* best diag : int dmaxO ;/* final diag */ int dna ;/* set if dna : main () */ int endgaps ;/* set if penalizing end gaps int gapx, gapy ;/* total gaps in seqs int lenO, lenl ;/* seq lens */ int ngapx, ngapy total size of gaps int smax score : int *xbm ;/* bitmap for matching long offset ;/* current offset in jmp file */ struct diag *dx ;/* holds diagonals */ struct path pp ;/* holds path for seqs char *callcoO, *malloc (), ; char () ; Table 1 /* Needleman-Wunsch alignment program usage : progs filel file2 where filel and file2 are two dna or two protein sequences.

The sequences can be in upper-or lower-case an may contain ambiguity Any lines beginning with' ;','>'or'<'are ignored * Max file length is 65535 (limited by unsigned short x in the jmp struct) A sequence with 1/3 or more of its elements ACGTU is assumed to be DNA Output is in the file"align. out" * The program may create a tmp file to hold info about traceback.

* Original version developed under BSD 4. 3 on a vax 8650 */ h" #include"day. h" [26] 1, 14, 2, 13, 0, 0, 4, 11, 0, 0, 12, 0, 3, 15, 0, 0, 0, 5, 6, 8, 8, 7, 9, 0, 10, 0 [26] 4, 8, 16, 32, 64, 1 « 15, 1 « 16, 1 « 17, 1 « 18, 1 « 19, 1 « 20, 1 « 21, 1 « 22, ('E'-'A')) l main (ac, av) main int ac ; char *av [] ; prog = av [0] ; if (ac ! fprintf (stderr,"usage : filel file2\n", prog) ; fprintf (stderr,"where filel and file2 are two dna or two protein sequences. \n") ; fprintf (stderr,"The sequences can be in upper-or ; fprintf (stderr,"Any lines beginning ignored\n") ; fprintf (stderr,"Output is in the file \"align. out\"\n") ; exit ; namex = av [l] ; namex = av [2] ; seqx [0] = getseq (namex ; seqx = getseq (namex ; xbm = (dna) : pbval ; endgaps = 0 ;/* 1 to penalize endgaps ="align. out";/* output file */ nw () ;/* fill in the matrix, get the possible jmps ;/* get the actual jmps */ print () ;/* print stats, alignment cleanup any tmp files Table 1 (cont') /* do the alignment, return best score : * dna : values in Fitch and Smith, PNAS, 80, 1382-1386, 1983 * pro : PAM 250 values When scores are equal, we prefer mismatches to any gap, prefer a new gap to extending an ongoing gap, and prefer a gap in seqx * to a gap in seq y.

nw () char *px, *py ; /* seqs and ptrs int *ndely, *dely keep track of dely int ndelx, delx ;/* keep track of delx int *tmp ;/* for swapping rowO, rowl int mis ;/* score for each type int insl ;/* insertion penalties register id ;/* diagonal index register ij; /* jmp index */ register *co10, *coll ;/* score for curr, last row register xx, yy ;/* index into seqs */ dx = (struct diag *) g calloc ("to get diags", (struct diag)) ; ndely = (int *) ("to sizeof (int)) ; dely = (int *) g calloc ("to get dely", lenl + 1, sizeof (int)) ; colO = (int *) g calloc ("to get colO", lenl + 1, sizeof ; coll = (int *) g calloc ("to get coll", sizeof ; insO = (dna) ? DINSO : PINSO ; = (dna) ? DINS1 : PINS1 ; smax =-10000 ; if (endgaps) { for (col0 [0] = dely [0] =- insO, yy = 1 ; yy < = lenl ; yy++) { col0 = dely = col0 [yy-1]-ins1 ; = yy ; col0 [0] = ;/* Waterman Bull Math Biol 84 else for (yy = 1 ; yy < = lenl ; dely ; /* fill in match matrix */ for (px = 1 ; xx < = lenO ; initialize first entry in col */ if (endgaps) if coll [0] = delx ; else coll [0] = delx = col0 ; ndelx = xx ; else { coll [0] = ; delx ; ndelx = ; Table 1 ... nw for (py = seqx [l], yy = 1 ; yy < = lenl ; mis = col0 [yy-1] ; if (dna) mis (xbm [*px-'A'] &xbm [*py-'A']) ? DMAT ; else mis += day ; /* update penalty for del in x seq ; favor new del over ongong del * ignore MAXGAP if weighting endgaps */ if (endgaps < MAXGAP) if (col0 > = dely [yy]) dely [yy] = col0 [yy]- ; = 1 ; } else { dely [yy]-= insl ; ndely + + ; } else { if > dely dely [yy] = col0 [yy]- ; ndely = 1 ; } else ndely [yy] + + ; /* update penalty for del in y seq ; * favor new del over ongong del */ if (endgaps ndelx < MAXGAP) if (coll [yy-l]-insO > = delx) delx = ; ndelx = 1 ; } else { ndelx+ + ; } else { if (coll [yy-1] - > = delx) delx = coll [yy-1]- ; ndelx = 1 ; } else ndelx+ + ; /* pick the maximum score ; we're favoring * mis over any del and delx over dely */ Table 1 (cont') ... nw ; if (mis > = delx && mis > = dely coll [yy] = mis ; else if (delx > = dely coll[yy] = delx ; ij = dx[id]. ijmp ; if (dx jp. n [O] && dna > = MAXJMP > dx x [ij] +MX) mis > dx [id]. score+DINSO)) dx ijmp++ ; if MAXJMP) writejmps ij = dx ; dx [id]. offset = offset ; offset sizeof (struct jmp) + sizeof (offset) ; dx [id] jp. n [ij] = ndelx ; dx [id]. jp. x [ij] = xx ; dx [id]. score = delx ; else { = ; ij = dx ; if (dx [id]. jp. n [O] && dna # # (ndely > = MAXJMP && xx > dx [id]. jp. > dx

score+DINSO)) { ; if > = MAXJMP) writejmps (id) ; ij = dx dx [id]. offset = offset ; offset + = sizeof (struct jmp) + sizeof (offset) ; dx jp. n [ij] =-ndely [yy] ; dx jp. x [ij] = xx ; dx score = dely [yy] ; if (xx = = lenO && yy < lenl) /* last col */ if (endgaps) coll [yy]-= ; if (coll [yy] > smax) { smax = coll [yy] ; dmax = id ; if (endgaps && xx < lenO) ; if (coll [yy-l] > smax) smax = coll [yy-1] ; dmax = id ; tmp = colO ; colO = coll ; coll = tmp ; (void) free ( (char *) ndely) ; (void) free ( (char *) dely) ; (void) free ( (char *) col0) ; (void) free ( (char *) coll) ; Table 1 visible outside this module * static : back best path, count matches : print () alignment of described in array p [] : a block of lines with numbers, stars : * out a number line : dumpblock () out a line (name, [num], seq, [num]) : dumpblock () * stars ()--put a line of stars : dumpblock () any path and prefix from a seqname */ #include"nw. h" #define SPC 3 #define P_LINE 256/* maximum output line #define space between name or num and seq extern day [26] [26] ; int olen ;/* set output line length */ FILE *fx ;/* output file int lx, firstgap, lastgap ;/* overlap if = fopen (ofile,"w")) fprintf : can't write prog, ofile) ; cleanup ; fprintf (fx,"<first sequence : (length \n", ; fprintf : %s (lengh = %d) \n", namex lenl) ; olen = 60 ; lx = lenO ; ly = lenl ; firstgap = lastgap = ; if (dmax < lenl-1) leading gap in x pp [O]. spc = firstgap = lenl-dmax-1 ; ; else if (dmax > lenl-1) leading gap in y pp spc = firstgap = dmax- ; Ix-= spc ; if (dmax0 < len0-10 {/* trailing gap in x lastgap = ; lastgap ; else if (dmaxO > len0-1 {/* trailing gap in y lastgap = (len0-1) ; ly-= lastgap ; (lx, ly, firstgap, lastgap) ; pr align () ; Table 1 /* * trace back the best path, count matches */ static getmat (lx, firstgap, lastgap) int ly ;/*"core" (minus endgaps) int firstgap, lastgap ;/* leading trailing overlap int il, sizO, sizl ; char outx [32] ; double pct ; register nO, nl ; register char *pO, *pl ; /* get total matches, score i0 = sizO = sizl ; pO + pp spc ; pl = seqx[1] + pp [0] spc ; nO = pp[1]. spc + 1 ; nl = pp[0]. spc + 1 ; nm = 0 ; while (*pO && *pl) if (sizO) p1+ + ; ; sizO--; else if (sizl) { ; ; siz1--; else if (xbm [*p0-'A']&xbm[*pl-'A']) ; if sizO = pp[0]. n [iO++l ; if (n1++ = = pp[1]. x [il]) sizl = pp[1]. n ; ; pl + + ; /* pet homology : penalizing endgaps, base is the shorter seq * else, knock off overhangs and take shorter core */ if (endgaps) = (lenO < lenl) ? len0 : lenl ; else lx = (lx < ly) ? 1x : ly ; pct = 100. * (double) lx ; fprintf (fx,"\n") ; fprintf (fx,"< % d match% s in an overlap of % d : %. 2f percent similarity\n", Table 1 (cont') fprintf : gapx) if (gapx) { (void) sprintf (outx," ngapx, (dna) (ngapx = = 1)? "":"s") ; fprintf outx) ; fprintf gaps in second sequence : gapy) ; if (gapy) { (void) sprintf (outx," ngapy, (dna) (ngapy = = 1)? "":"s") ; fprintf outx) ; if (dna) fprintf : %d (match = %d, mismatch = %d, gap enalty = %d + %d per base) \n", smax, DMAT, DMIS, DINSO, DINS1) ; else fprintf (fx, score : % d (Dayhoff PAM 250 matrix, gap penalty = % d + % d per residue) \n", smax, PINSO, PINS1) ; if (endgaps) fprintf (fx, : %d %s%s, right endgap : %d %s% s\n", firstgap, (dna) ?"base" :"residue", (firstgap == 1) lastgap, (dna) ?"base" :"residue", (lastgap == 1) ; else fprintf (fx,"< endgaps ; static nm ;/* matches in core--for checking static Imax ;/* lengths of stripped file names static ij index for a path */ static nc number at start of current line static ni ;/* current elem number--for gapping static siz [2] ; static char *ps [2] to current element static char *po to next output char slot static char out ;/* output line static char star ;/* set by /* * print alignment of described in struct path pp [] */ static int nn ;/* char count int more ; register i ; for (i = lmax = ; i < 2 ; nn = stripname (namex [i]) ; if (nn > Imax = nn ; nc [i] = 1 ; ni [i] = 1 ; = ; ps [i] = seqx [i] ; po [i] = out [i] ; Table 1 for = more = 1 ; more ;) pr align for (i = more = 0 ; i < 2 ; /* * do we have more of this sequence ? */ if continue ; more++ ; if (pp space pp[i].spc--; else if (siz [i]) in a gap *po [i]++ = '-'; siz [i]--; we're putting a seq element */ *po[i] = *ps [i] ; if (islower (*ps [i])) *ps [i] = toupper (*ps [i]) ; po [i] + + ; [i] + + ; /* * are we at next gap for this seq ? I/ if (ni = = pp[i].x[ij[i]) { /* * we need to merge all gaps * at this location */ siz [i] = pp[i]. n [ij [i] ++] ; while (ni [i] ==pp [i]. x [ij [i]]) siz [i] n [ij [i] ++] ; ni[i]++ ; if && nn) ; for (i = ; i < 2 ; po[i] = out [i] ; nn=0 ; * dump a block of lines, including numbers, stars : */ static dumpblock { register i ; for (i = 0 ; i < 2 ; i++) *po[i]- = '\0'; Table 1 ... dumpblock (void) putc ('\n', fx) ; for (i 0 ; i < 2 ; i++) if (*out [i] && (*out [i] !=" *(po[i] = ")) { if (i == 0) nums (i) ; if (i == 0 *out[1]) stars () ; putline (i) ; if (i = = 0 && *out[1]) fprintf (fx, star) ; if nums (i) ; put out a number line : dumpblock () */ static nums (ix) nums int ix ;/* index in out [] holding seq line char nline ; register i, j ; register char *pn, *px, *py ; for (pn = nline, i ; i < ; *pn ="; for (i nc [ix], py out [ix] ; *py ; +, pn+ +) { if (*py = = " *py = = '-') *pn = ", else { j (i < ?-i : i ; for (px = pn ; j ; j/= 10, px--) if (i < *px = '-' ; else else i++' } } *pn = '\0'; nc [ix] = i ; for (pn = nline ; *pn ; (void) putc (*pn, fx) ; (void) putc ('\n', fx) ; put out a line (name, [num], seq, [num]) : dumpblock () */ static putline (ix)

putline Table 1 putline int i ; register char *px ; for (px = namex [ix], i = ; *px && *px (void) putc (*px, fx) ; for i < ; (void) putc ('', fx) ; /* these count from 1 : * is current element (from 1) nc [] is number at start of current line for (px = out [ix] ; *px ; (void) putc (*px&Ox7F, fx) ; (void) putc ('\n', ; a line of stars (seqs always in out out : dumpblockQ */ static stars () stars { int i ; register char *pO, *pl, cx, *px ; if *out [O] ! *out [1] (po return ; ; for (i = lmax+p SPC ; i ; i--) ="; for (pO = out[0], p1 = out[1]; *p0 && *pl ; if (isalpha (*pO) && isalpha (*pl)) { if (xbm &xbm [*pl-'A']) cx = '*'; ; [*pl-'A'] > cx = '.' ; else else = ex ; *px+ + = '\n'; *px = '\0'; Table 1 (cont') /* * strip path or prefix from pn, return len : static stripname (pn) stripname char *pn ;/* file name (may be path) register char *px, *py ; py = 0; for (px = pn ; *px ; if py = px + 1 ; if (void) strcpy (pn, py) ; return (strlen (pn)) ; Table 1 * cleanup ()-- cleanup any tmp file in seq, set dna, len, maxlen error * readjmpsQ--get the good jmps ; from tmp file if necessary a filled array of jmps to a tmp file : #include"nw. h" #include char *jname file for jmps */ FILE *fj ; int cleanup () ;/* cleanup tmp file */ long ; /* * remove any tmp file if we blow cleanup (i) cleanup int i ; if (fj) (void) ; exit (i) ; * read, return ptr to seq, set dna, len, maxlen * skip lines starting with ';', '<', or '>' * seq in upper or lower case */ char getseq (file, len) getseq char *file ;/* file name int *len ;/* seq len char line [1024], *pseq ; register char *px, *py ; int natgc, tlen ; FILE *fp ; if = fopen (file,"r")) = = 0) { fprintf : prog, file) ; exit ; tlen = natgc = ; while (fgets (line, 1024, if (*line continue ; for (px = line ; if (isupper (*px)) tlen+ + ; if = malloc ( (unsigned) (tlen+6))) = =0) { fprintf (stderr,"% s : malloc () failed to get % d bytes for prog, tlen+6, file) ; exit ; pseq [0] = pseq = pseq [2] = pseq [3] = '\0' ; Table 1 ... getseq py = pseq + 4 ; *len = tlen ; rewind (fp) ; while (fgets (line, 1024, fp)) if (*line continue ; for (px = line ; *px! = '\n' ; px++) { if (isupper (*px)) *py++ = *px ; else if (islower (*px)) *py++ = toupper (*px) ; if (index ("ATGCU", * (py-1))) natgc++ ; *py++ = '\0'; *py = '\0'; (void) fclose (fp) ; dna = natgc > (tlen/3) ; return (pseq+4) ; char g_calloc (msg, nx, sz) gcalloc char *msg ;/* program, calling routine int nx, sz ;/* number and size of elements char *px, ; if = ( (unsigned) nx, (unsigned) sz)) if (*msg) fprintf (stderr,"% s : failed \n", prog, msg, nx, sz) ; exit ; return (px) ; * get final jmps from dx or tmp file, set pp [], reset dmax : maint */ int ; int siz, il ; register i, j, xx ; (void) fclose ; if ( (fd = open (jname, O RDONLY, 0)) < fprintf : can't jname) ; cleanup ; for (i = iO = il = dmaxO = dmax, xx = lenO ; ; while (1) for (j = dx [dmax]. ijmp ; > = && dx > = xx ; Table 1 (cont') ... readjmps if < && dx [dmax]. offset &&fj) { (void) lseek (fd, dx [dmax]. offset, ; (void) read (fd, (char *) &dx [dmax]. jp, sizeof ; (void) read (char &dx [damax]. offset, sizeof (dx [dmax]. offset)) ; dx [dmax]. ijmp = MAXJMP-1 ; else break ; if (i > = JMPS) { fprintf : too many gaps in prog) ; cleanup ; if (j > = 0) { siz = dx [dmax]. jp. ; xx = dx [dmax]. jp. dmax siz ; if (siz < gap in second seq pp n [il] = -siz ; xx += siz ; */ pp x [il] = xx-dmax + lenl-1 ; gapy++ ; ngapy-= siz ; /* ignore MAXGAP when doing endgaps */ siz = (-siz < ?-siz : MAXGAP ; il + + ; else if (siz > {/* gap in first seq pp [0] n [io] = siz ; pp [0].x[io] = xx ; ; ngapx siz ; /* ignore MAXGAP when doing endgaps siz = (siz < MAXGAP endgaps) ? siz : MAXGAP ; ; else break ; /* reverse the order of jmps */ for (j = j < iO ; j++, i0--) { i = pp [O]. n [j] ; pp [0]. n [iO] ; pp [Oj. n [io] = i ; i = pp[0].x[j]; pp[0].x[u] = pp[0].x[i0] ; pp [0]. x [i0] = i ; for (j = 0, il-- ; j < il ; i = pp [1].n[j] ; pp n[j] = pp[1].n[i1] ; pp [1]. n [il] = i ; i = pp[1].x[j] ; = ; pp [il] = i ; if (fd (void) close (fd) ; if (fj) { (void) unlink(jname) ; fj = 0 ; offset = ; Table 1 (cont') * write a filled jmp struct offset of the prev one (if any) : */ writejmps (ix) writejmps int ix ; char ; if if < { fprintf : can't prog, jname) ; cleanup ; if = fprintf(stderr, "%s : can't write % s\n", prog, jname) ; exit ; (void) fwrite ( (char *) &dx jp, sizeof 1, ; (void) fwrite ( (char *) &dx [ix]. offset, sizeof (dx [ix]. offset), 1, ; Table 2 PRO (Length = 15 amino acids) Comparison Protein XXXXXYYYYYYY (Length = 12 amino acids) % amino acid sequence identity = (the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) 5 divided by 15 = 33. Table 3 PRO (Length = 10 amino acids) Comparison Protein XXXXXYYYYYYZZYZ (Length = 15 amino acids) % amino acid sequence identity (the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the PRO polypeptide) 5 divided by 10 = Table 4 PRO-DNA NNNNNNNNNNNNN (Length = 14 nucleotides) Comparison DNA NNNNNNLLLLLLLLL (Length = 16 nucleotides) % nucleic acid sequence identity = (the number of identically matching nucleotides between the two nucleic acid sequences as

determined by ALIGN- 2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) 6 divided by 14 = 42. 9% Table 5 PRO-DNA NNNNNNNNNNNN (Length = 12 nucleotides) Comparison DNA NNNNLLLVV (Length = 9 nucleotides) % nucleic acid sequence identity = (the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN- 2) divided by (the total number of nucleotides of the PRO-DNA nucleic acid sequence) 4 divided by 12 II. Compositions and Methods of the Invention A. Full-Length PRO The present invention provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as PRO polypeptides. In particular, cDNAs encoding various PRO polypeptides have been identified and isolated, as disclosed in further detail in the Examples below. It is noted that proteins produced in separate expression rounds may be given different PRO numbers but the UNQ number is unique for any given DNA and the encoded protein, and will not be changed. However, for sake of simplicity, in the present specification the protein encoded by the full length native nucleic acid molecules disclosed herein as well as all further native homologues and variants included in the foregoing definition of PRO, will be referred to as"PRO/number", regardless of their origin or mode of preparation.

As disclosed in the Examples below, various cDNA clones have been deposited with the ATCC. The actual nucleotide sequences of those clones can readily be determined by the skilled artisan by sequencing of the deposited clone using routine methods in the art. The predicted amino acid sequence can be determined from the nucleotide sequence using routine skill. For the PRO polypeptides and encoding nucleic acids described herein, Applicants have identified what is believed to be the reading frame best identifiable with the sequence information available at the time.

B. PRO Polypeptide Variants In addition to the full-length native sequence PRO polypeptides described herein, it is contemplated that PRO variants can be prepared. PRO variants can be prepared by introducing appropriate nucleotide changes into the PRO DNA, and/or by synthesis of the desired PRO polypeptide. Those skilled in the art will appreciate that amino acid changes may alter post-translational processes of the PRO, such as changing the number or position of glycosylation sites or altering the membrane anchoring characteristics.

. Variations in the native full-length sequence PRO or in various domains of the PRO described herein, can be made, for example, using any of the techniques and guidelines for conservative and non-conservative mutations set forth, for instance, in U. S. Patent No. 5, 364, 934. Variations may be a substitution, deletion or insertion of one or more codons encoding the PRO that results in a change in the amino acid sequence of the PRO as compared with the native sequence PRO. Optionally the variation is by substitution of at least one amino acid with any other amino acid in one or more of the domains of the PRO. Guidance in determining which amino acid residue may be inserted, substituted or deleted without adversely affecting the desired activity may be found by comparing the sequence of the PRO with that of homologous known protein molecules and minimizing the number of amino acid sequence changes made in regions of high homology. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine with a serine, i. e., conservative amino acid replacements. Insertions or deletions may optionally be in the range of about 1 to 5 amino acids. The variation allowed may be determined by systematically making insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the full-length or mature native sequence.

PRO polypeptide fragments are provided herein. Such fragments may be truncated at the N-terminus or C-terminus, or may lack internal residues, for example, when compared with a full length native protein.

Certain fragments lack amino acid residues that are not essential for a desired biological activity of the

PRO polypeptide.

PRO fragments may be prepared by any of a number of conventional techniques. Desired peptide fragments may be chemically synthesized. An alternative approach involves generating PRO fragments by enzymatic digestion, e. g., by treating the protein with an enzyme known to cleave proteins at sites defined by particular amino acid residues, or by digesting the DNA with suitable restriction enzymes and isolating the desired fragment. Yet another suitable technique involves isolating and amplifying a DNA fragment encoding a desired polypeptide fragment, by polymerase chain reaction (PCR). Oligonucleotides that define the desired termini of the DNA fragment are employed at the 3'primers in the PCR. Preferably, PRO polypeptide fragments share at least one biological and/or immunological activity with the native PRO polypeptide disclosed herein.

In particular embodiments, conservative substitutions of interest are shown in Table 6 under the heading of preferred substitutions. If such substitutions result in a change in biological activity, then more substantial changes, denominated exemplary substitutions in Table 6, or as further described below in reference to amino acid classes, are introduced and the products screened.

Table 6 Original Exemplary Preferred Residue Substitutions Substitutions Ala (A) val ; leu ; ile val Arg (R) lys ; gln ; asn lys Asn (N) gln ; his ; lys ; arg gln Asp (D) glu glu Cys (C) ser ser Gln (Q) asn asn Glu (E) asp asp Gly (G) pro ; ala ala His (H) asn ; gln ; lys ; arg arg Ile leu ; val ; met ; ala ; phe ; norleucine leu Leu (L) norleucine ; ile ; val ; met ; ala ; phe ile Lys arg ; gln ; asn arg Met (M) leu ; phe ; ile leu Phe (F) leu ; val ; ile ; ala ; tyr leu Pro (P) ala ala Ser (s) thr thr Thr (T) ser ser Trp (W) tyr ; phe tyr Tyr (Y) trp ; phe ; thr ; ser phe Val (V) ile ; leu ; met ; phe ; ala ; norleucine leu Substantial modifications in function or immunological identity of the PRO polypeptide are accomplished by selecting substitutions that differ significantly in their effect on maintaining (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties : (1) hydrophobic : norleucine, met, ala, val, leu, ile ; (2) neutral hydrophilic : cys, ser, thr ; (3) acidic : asp, glu ; (4) basic : asn, gln, his, lys, arg ; (5) residues that influence chain orientation : gly, pro ; and (6) aromatic : trp, tyr, phe.

Non-conservative substitutions will entail exchanging a member of one of these classes for another class.

Such substituted residues also may be introduced into the conservative substitution sites or, more preferably, into the remaining (non-conserved) sites.

The variations can be made using methods known in the art such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Site-directed mutagenesis [Carter et al., Nucl.

Acids Res., 13 : 4331 (1986) ; Zoller et Nucl. Acids Res., : 6487 (1987)], cassette mutagenesis [Wells et al., Gene, : 315 (1985)], restriction selection mutagenesis [Wells et al., Philos. Trans. R. Soc. London SerA, 317 : 415 (1986)] or other known techniques can be performed on the cloned DNA to produce the PRO variant DNA.

Scanning amino acid analysis can also be employed to identify one or more amino acids along a contiguous sequence. Among the preferred scanning amino acids are relatively small, neutral amino acids. Such amino acids include alanine, glycine, serine, and cysteine. Alanine is typically a preferred scanning amino acid among this group because it eliminates the side-chain beyond the beta-carbon and

is less likely to alter the main- chain conformation of the variant [Cunningham and Wells, Science, 244 : 1081-1085 (1989)]. Alanine is also typically preferred because it is the most common amino acid. Further, it is frequently found in both buried and exposed positions [Creighton, The Proteins, (W. H. Freeman & Co., N. Y.) ; Chothia, J. Mol. Biol., 150 : 1 (1976)]. If alanine substitution does not yield adequate amounts of variant, an isoteric amino acid can be used.

C. Modifications of PRO Covalent modifications of PRO are included within the scope of this invention. One type of covalent modification includes reacting targeted amino acid residues of a PRO polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or the N-or C-terminal residues of the PRO.

Derivatization with bifunctional agents is useful, for instance, for crosslinking PRO to a water-insoluble support matrix or surface for use in the method for purifying anti-PRO antibodies, and vice-versa. Commonly used crosslinking agents include, e. g., (diazoacetyl)-2-phenylethane, glutaraldehyde, esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including esters such as 3, 3'-dithiobis bifunctional maleimides such as 8-octane and agents such as

Other modifications include deamidation of glutaminyl and asparaginyl residues to the corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the a-amino groups of lysine, arginine, and histidine side chains [T. E. Creighton, Proteins : Structure and Molecular Properties, W. H. Freeman & Co., San Francisco, pp. 79-86 (1983)], acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

Another type of covalent modification of the PRO polypeptide included within the scope of this invention comprises altering the native glycosylation pattern of the polypeptide."Altering the native glycosylation pattern" is intended for purposes herein to mean deleting one or more carbohydrate moieties found in native sequence PRO (either by removing the underlying glycosylation site or by deleting the glycosylation by chemical and/or enzymatic means), adding one or more glycosylation sites that are not present in the native sequence PRO.

In addition, the phrase includes qualitative changes in the glycosylation of the native proteins, involving a change in the nature and proportions of the various carbohydrate moieties present.

Addition of glycosylation sites to the PRO polypeptide may be accomplished by altering the amino acid sequence. The alteration may be made, for example, by the addition of, or substitution by, one or more serine or threonine residues to the native sequence PRO (for O-linked glycosylation sites). The PRO amino acid sequence may optionally be altered through changes at the DNA level, particularly by mutating the DNA encoding the PRO polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

Another means of increasing the number of carbohydrate moieties on the PRO polypeptide is by chemical or enzymatic coupling of glycosides to the polypeptide. Such methods are described in the art, e. g., in WO 87/05330 published 11 September 1987, and in Aplin and Wriston, CRC Crit. Rev. Biochem., pp. 259-306 (1981).

Removal of carbohydrate moieties present on the PRO polypeptide may be accomplished chemically or enzymatically or by mutational substitution of codons encoding for amino acid residues that serve as targets for glycosylation. Chemical deglycosylation techniques are known in the art and described, for instance, by Hakimuddin, et Arch. Biochem. 259 : 52 (1987) and by Edge et Anal. Biochem., 118 : 131

(1981). Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo-and exo-glycosidases as described by Thotakura et al., Meth. 138 : 350 (1987).

Another type of covalent modification of PRO comprises linking the PRO polypeptide to one of a variety of nonproteinaceous polymers, e. g., polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U. S. Patent Nos. 4, 640, ; 4, 496, 689 ; 4, 301, 144 ; 4, 670, 417 ; 4, 791, 192 or 4, 179, 337.

The PRO of the present invention may also be modified in a way to form a chimeric molecule comprising PRO fused to another, heterologous polypeptide or amino acid sequence.

In one embodiment, such a chimeric molecule comprises a fusion of the PRO with a tag polypeptide which provides an epitope to which an anti-tag antibody can selectively bind. The epitope tag is generally placed at the amino-or carboxyl-terminus of the PRO. The presence of such epitope-tagged forms of the PRO can be detected using an antibody against the tag polypeptide. Also, provision of the epitope tag enables the PRO to be readily purified by affinity purification using an anti-tag antibody or another type of affinity matrix that binds to the epitope tag. Various tag polypeptides and their respective antibodies are well known in the art. Examples include poly-histidine (poly-his) or poly-histidine-glycine (poly-his-gly) tags ; the flu HA tag polypeptide and its antibody 12CA5 [Field et al., Mol. Cell. 8 : 2159-2165 ; the c-myc tag and the 3C7, G4, B7 and antibodies thereto [Evan et al., Molecular and Cellular Biology, : 3610-3616 (1985)] ; and the Herpes Simplex virus glycoprotein D (gD) tag and its antibody [Paborsky et Protein Engineering, 3 (6) : 547- 553 (1990)]. Other tag polypeptides include the Flag-peptide [Hopp et al., BioTechnology, : 1204-1210 (1988)] ; the KT3 epitope peptide [Martin et al., Science, 255 : 192-194 ; an a-tubulin epitope peptide [Skinner et al., J. Biol. 266 : 15163-15166 (1991)] ; and the T7 gene 10 protein peptide tag et al., Proc. Natl. Acad. Sci. USA, 87 : 6393-6397 (1990)].

In an alternative embodiment, the chimeric molecule may comprise a fusion of the PRO with an immunoglobulin or a particular region of an immunoglobulin. For a bivalent form of the chimeric molecule (also referred to as such a fusion could be to the Fc region of an IgG molecule. The Ig fusions preferably include the substitution of a soluble (transmembrane domain deleted or inactivated) form of a PRO polypeptide in place of at least one variable region within an Ig molecule. In a particularly preferred embodiment, the immunoglobulin fusion includes the hinge, CH2 and CH3, or the hinge, CH2 and CH3 regions of an molecule. For the production of immunoglobulin fusions see also US Patent No. 5, 428, 130 issued June 27, 1995.

D. Preparation of PRO The description below relates primarily to production of PRO by culturing cells transformed or transfected with a vector containing PRO nucleic acid. It is, of course, contemplated that alternative methods, which are well known in the art, may be employed to prepare PRO. For instance, the PRO sequence, or portions thereof, may be produced by direct peptide synthesis using solid-phase techniques [see, e. g., Stewart et al., Solid- Phase H. Freeman Co., San Francisco, CA (1969) ; Merrifield, Am. Chem. 85 : 2149-2154 (1963)]. In vitro protein synthesis may be performed using manual techniques or by automation.

Automated synthesis may be accomplished, for instance, using an Applied Biosystems Peptide Synthesizer (Foster City, CA) using manufacturer's instructions. Various portions of the PRO may be chemically synthesized separately and combined using chemical or enzymatic methods to produce the full-length PRO.

1. Isolation of DNA Encoding PRO DNA encoding PRO may be obtained from a cDNA library

prepared from tissue believed to possess the PRO and to express it at a detectable level. Accordingly, human PRO DNA can be conveniently obtained from a cDNA library prepared from human tissue, such as described in the Examples. The PRO-encoding gene may also be obtained from a genomic library or by known synthetic procedures (e. g., automated nucleic acid synthesis).

Libraries can be screened with probes (such as antibodies to the PRO or oligonucleotides of at least about 20-80 bases) designed to identify the gene of interest or the protein encoded by it. Screening the cDNA or genomic library with the selected probe may be conducted using standard procedures, such as described in Sambrook et Molecular Cloning : A Laboratory Manual (New York : Cold Spring Harbor Laboratory Press, 1989). An alternative means to isolate the gene encoding PRO is to use PCR methodology [Sambrook et al., supra ; Dieffenbach et al., PCR Primer : A Laboratory Manual (Cold Spring Harbor Laboratory Press, 1995)].

The Examples below describe techniques for screening a cDNA library. The oligonucleotide sequences selected as probes should be of sufficient length and sufficiently unambiguous that false positives are minimized.

The oligonucleotide is preferably labeled such that it can be detected upon hybridization to DNA in the library being screened. Methods of labeling are well known in the art, and include the use of radiolabels like ATP, biotinylation or enzyme labeling. Hybridization conditions, including moderate stringency and high stringency, are provided in Sambrook et al., supra.

Sequences identified in such library screening methods can be compared and aligned to other known sequences deposited and available in public databases such as GenBank or other private sequence databases.

Sequence identity (at either the amino acid or nucleotide level) within defined regions of the molecule or across the full-length sequence can be determined using methods known in the art and as described herein.

Nucleic acid having protein coding sequence may be obtained by screening selected cDNA or genomic libraries using the deduced amino acid sequence disclosed herein for the first time, and, if necessary, using conventional primer extension procedures as described in Sambrook et al., supra, to detect precursors and processing intermediates of that may not have been reverse-transcribed into cDNA.

2. Selection and Transformation of Host Cells Host cells are transfected or transformed with expression or cloning vectors described herein for PRO production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. The culture conditions, such as media, temperature, pH and the like, can be selected by the skilled artisan without undue experimentation. In general, principles, protocols, and practical techniques for maximizing the productivity of cell cultures can be found in Mammalian Cell Biotechnology : a Practical Approach, M. Butler, ed. (IRL Press, 1991) and Sambrook et al., supra.

Methods of eukaryotic cell transfection and prokaryotic cell transformation are known to the ordinarily skilled artisan, for example, and electroporation. Depending on the host cell used, transformation is performed using standard techniques appropriate to such cells. The calcium treatment employing calcium chloride, as described in Sambrook et al., supra, or electroporation is generally used for prokaryotes. Infection with Agrobacterium is used for transformation of certain plant cells, as described by Shaw et al., Gene, 23 : 315 (1983) and WO published 29 June For mammalian cells without such cell walls, the calcium phosphate precipitation method of Graham and van der Eb, Virology, : 456- 457

(1978) can be employed. General aspects of mammalian cell host system transfections have been described in U. S. Patent No. 4, 399, 216. Transformations into yeast are typically carried out according to the method of Van Solingen et al., J. 130 : 946 (1977) and Hsiao et al., Proc. Natl. Acad. Sci. (USA), 76 : 3829 (1979).

However, other methods for introducing DNA into cells, such as by nuclear microinjection, electroporation, bacterial protoplast fusion with intact cells, or polycations, e. g., polybrene, may also be used. For various techniques for transforming mammalian cells, see Keown et Methods in 527-537 (1990) and Mansour et al., Nature, 336 : 348-352 (1988).

Suitable host cells for cloning or expressing the DNA in the vectors herein include prokaryote, yeast, or higher eukaryote cells. Suitable prokaryotes include but are not limited to eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as E. coli. Various coli strains are publicly available, such as E. coli K12 strain MM294 (ATCC 31, 446) ; E. coli X1776 (ATCC 31, 537) ; E. coli strain W3110 (ATCC 27, 325) and K5 772 (ATCC 53, 635). Other suitable prokaryotic host cells include Enterobacteriaceae such as Escherichia, e. g., E. coli, Enterobacter, Erwinia, Klebsiella, Proteus, Salmonella, e. g., Salmonella and Shigella, as well as Bacilli such as B. subtilis and B. (e. g., 41P disclosed in DD 266, 710 published 12 April 1989), Pseudomonas such as and These examples are illustrative rather than limiting.

Strain is one particularly preferred host or parent host because it is a common host strain for recombinant DNA product fermentations. Preferably, the host cell secretes minimal amounts of proteolytic enzymes. For example, strain may be modified to effect a genetic mutation in the genes encoding proteins endogenous to the host, with examples of such hosts including E. strain 1A2, which has the complete genotype ; E. strain 9E4, which has the complete genotype ; E. coli strain 27C7 (ATCC 55, 244), which has the complete genotype ; E. coli ; E. coli W3110 strain 40B4, which is strain 37D6 with a non-kanamycin resistant deletion mutation and an E. coli strain having mutant periplasmic protease disclosed in U. S. Patent No. 4, 946, 783 issued 7 August 1990.

Alternatively, in vitro methods of cloning, e. g., PCR or other nucleic acid polymerase reactions, are suitable.

In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for PRO-encoding vectors. Saccharomyces cerevisiae is a commonly used lower eukaryotic host microorganism. Others include (Beach and Nurse, Nature, 290 : 140 ; EP 139, 383 published 2 May 1985) ; Kluyveromyces hosts (U. S. Patent No. 4, 943, 529 ; Fleer et al., 9 : 968-975 (1991)) such as, e. CBS683, CBS4574 ; Louvencourt et al., J. Bacteriol., 154 (2) : 737-742 fragilis (ATCC 12, 424), bulgaricus (ATCC 16, 045), wickeramii (ATCC 24, 178), K. (ATCC 56, 500), drosophilarum (ATCC 36, 906 ; Van den Berg et al., : 135 (1990)), and ; yarrowia (EP 402, 226) ; Pichia pastoris (EP 183, 070 ; et al., J. Basic Microbiol., 28 : 265-278 [1988]) ; (EP 244, 234) ; Neurospora crassa (Case et al., Proc. Natl. Acad. Sci. : 5259-5263 [1979]) ; Schwanniomyces such as Schwanniomyces occidentalis (EP 394, 538 published 31 October 1990) ; and filamentous fungi such as, e. g., Neurospora, 91/00357 published 10 January 1991), and Aspergillus hosts such as A. nidulans (Ballance et al., Biochem. Res. : 284-289 [1983] ; Tilburn et al., Gene, 26 : 205-221 [1983] ; Yelton et al., Proc. Natl. Acad. Sci. USA, : 1470-1474 [1984]) and A. niger (Kelly and Hynes, EMBO J., 4 : 475-479 yeasts are suitable herein and include, but are not limited to, yeast capable of growth on methanol selected from the genera consisting of Hansenula, Candida, Pichia, Saccharomyces, Torulopsis, and Rhodotorula. A list of specific species that are exemplary of this class of yeasts may be found in C. Anthony, The Biochemistry of 269 (1982).

Suitable host cells for the expression of glycosylated PRO are derived from multicellular organisms.

Examples of invertebrate cells include insect cells such as Drosophila S2 and Spodoptera Sf9, as well as plant cells. Examples of useful mammalian host cell lines include Chinese hamster ovary (CHO) and COS cells. More specific examples include monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651) ; human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al., J. Gen Virol., 36 : 59 (1977)) ; Chinese hamster ovary cells/-DHFR (CHO, Urlaub and Chasin, Proc. Natl. Acad. Sci. USA, 77 : 4216 ; mouse sertoli cells (TM4, Mather, Biol. Reprod., 23 : 243-251 (1980)) ; human lung cells (W138, ATCC CCL 75) ; human liver cells (Hep G2, HB 8065) ; and mouse mammary tumor (MMT 060562, ATCC The selection of the appropriate host cell is deemed to be within the skill in the art.

3. Selection and Use of a Repliable Vector The nucleic acid (e. g., cDNA or genomic DNA) encoding PRO may be inserted into a replicable vector for cloning (amplification of the DNA) or for expression. Various vectors are publicly available. The vector may, for example, be in the form of a plasmid, cosmid, viral particle, or phage. The appropriate nucleic acid sequence may be inserted into the vector by a variety of procedures. In general, DNA is inserted into an appropriate restriction endonuclease site (s) using techniques known in the art. Vector components generally include, but are not limited to, one or more of a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence. Construction of suitable vectors containing one or more of these components employs standard ligation techniques which are known to the skilled artisan.

The PRO may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, which may be a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the PRO-encoding DNA that is inserted into the vector. The signal sequence may be a prokaryotic signal sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, or heat-stable enterotoxin II leaders. For yeast secretion the signal sequence may be, e. g., the yeast invertase leader, alpha factor leader (including Saccharomyces and a-factor leaders, the latter described in U. S. Patent No. 5, 010, 182), or acid phosphatase leader, the albicans glucoamylase leader (EP 362, 179 published 4 April 1990), or the signal described in WO 90/13646 published 15 November 1990. In mammalian cell expression, mammalian signal sequences may be used to direct secretion of the protein, such as signal sequences from secreted polypeptides of the same or related species, as well as viral secretory leaders.

Both expression and cloning vectors contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells. Such sequences are well known for a variety of bacteria, yeast, and viruses.

The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the plasmid origin is suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV or BPV) are useful for cloning vectors in mammalian cells.

Expression and cloning vectors will typically contain a selection gene, also termed a selectable marker.

Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, e. g., neomycin, methotrexate, or tetracycline, (b) complement deficiencies, or (c) supply critical nutrients not available from complex media, e. g., the gene encoding D-alanine racemase for Bacilli.

An example of suitable selectable markers for mammalian cells are those that enable the identification of cells competent to take up the PRO-encoding nucleic acid, such as DHFR or thymidine kinase. An appropriate host cell when wild-type DHFR is employed is the CHO cell line deficient in DHFR

activity, prepared and propagated as described by Urlaub et al., Proc. Natl. Acad. Sci. USA, 77 : 4216 (1980). A suitable selection gene for use in yeast is the gene present in the yeast plasmid YRp7 [Stinchcomb et al., Nature, 282 : 39 (1979) ; Kingsman et Gene, 7 : 141 (1979) ; Tschemper et al., Gene, 10 : 157 (1980)]. The gene provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example, ATCC No.

44076 or PEP4-1 [Jones, Genetics, 85 : 12 (1977)].

Expression and cloning vectors usually contain a promoter operably linked to the PRO-encoding nucleic acid sequence to direct synthesis. Promoters recognized by a variety of potential host cells are well known. Promoters suitable for use with prokaryotic hosts include the and lactose promoter systems [Chang et al., Nature, 275 : 615 (1978) ; Goeddel et Nature, 281 : 544 (1979)], alkaline phosphatase, a tryptophan (trp) promoter system [Goeddel, Nucleic Acids Res., 8 : 4057 ; EP 36, 776], and hybrid promoters such as the tac promoter et al., Proc. Natl. Acad. Sci. USA, 80 : 21-25 (1983)]. Promoters for use in bacterial systems also will contain a Shine-Dalgarno (S. D.) sequence operably linked to the DNA encoding PRO.

Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase [Hitzeman et al., J. Biol. Chem., 255 : 2073 (1980)] or other glycolytic enzymes [Hess et al., J. Adv. Enzyme 7 : 149 (1968) ; Holland, Biochemistry, 17 : 4900 (1978)], such as enolase, glyceraldehyde-3-phosphate dehydrogenase, pyruvate decarboxylase, glucose-6- phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and

Other yeast promoters, which are inducible promoters having the additional advantage of transcription controlled by growth conditions, are the promoter regions for alcohol dehydrogenase 2, isocytochrome C, acid phosphatase, degradative enzymes associated with nitrogen metabolism, metallothionein, glyceraldehyde-3- phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization. Suitable vectors and promoters for use in yeast expression are further described in EP 73, 657.

PRO transcription from vectors in mammalian host cells is controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus (UK 2, 211, 504 published 5 July 1989), adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus and Simian Virus 40 (SV40), from heterologous mammalian promoters, e. g., the actin promoter or an immunoglobulin promoter, and from heat-shock promoters, provided such promoters are compatible with the host cell systems.

Transcription of a DNA encoding the PRO by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancers are cis-acting elements of DNA, usually about from 10 to 300 bp, that act on a promoter to increase its transcription. Many enhancer sequences are now known from mammalian genes (globin, elastase, albumin, a-fetoprotein, and insulin). Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the late side of the replication origin (bp 100- 270), the early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. The enhancer may be spliced into the vector at a position 5'or 3'to the PRO coding sequence, but is preferably located at a site 5'from the promoter.

Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5'and,

occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the encoding PRO.

Still other methods, vectors, and host cells suitable for adaptation to the synthesis of PRO in recombinant Nature, 293 : 620-625 ; 281 : 40- 46 (1979) ; EP 117, 060 ; and EP 117, 058.

4. Detecting Gene Gene amplification and/or expression may be measured in a sample directly, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription Natl.

Acad. Sci. USA, 77 : 5201-5205 (1980)], dot blotting (DNA analysis), or in situ hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes. The antibodies in turn may be labeled and the assay may be carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected.

Gene expression, alternatively, may be measured by immunological methods, such as staining of cells or tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native sequence PRO polypeptide or against a synthetic peptide based on the DNA sequences provided herein or against exogenous sequence fused to PRO DNA and encoding a specific antibody epitope.

5. Purification of Polypeptide Forms of PRO may be recovered from culture medium or from host cell lysates. If membrane-bound, it can be released from the membrane using a suitable detergent solution (e. g. Triton-X 100) or by enzymatic cleavage. Cells employed in expression of PRO can be disrupted by various physical or chemical means, such as freeze-thaw cycling, sonication, mechanical disruption, or cell lysing agents.

It may be desired to purify PRO from recombinant cell proteins or polypeptides. The following procedures are exemplary of suitable purification procedures : by fractionation on an ion-exchange column ; ethanol precipitation ; reverse phase HPLC ; chromatography on silica or on a cation-exchange resin such as DEAE ; chromatofocusing ; SDS-PAGE ; ammonium sulfate precipitation ; gel filtration using, for example, Sephadex G-75 ; protein A Sepharose columns to remove contaminants such as IgG ; and metal chelating columns to bind epitope- tagged forms of the PRO. Various methods of protein purification may be employed and such methods are known in the art and described for example in Deutscher, Methods in 182 (1990) ; Scopes, Protein Purification : Principles and Practice, Springer-Verlag, New York The purification step (s) selected will depend, for example, on the nature of the production process used and the particular PRO produced.

E. Uses for PRO Nucleotide sequences (or their complement) encoding PRO have various applications in the art of molecular biology, including uses as hybridization probes, in chromosome and gene mapping and in the generation of anti-sense RNA and DNA. PRO nucleic acid will also be useful for the preparation of PRO polypeptides by the recombinant techniques described herein.

The full-length native sequence PRO gene, or portions thereof, may be used as hybridization probes for a cDNA library to isolate the full-length PRO cDNA or to isolate still other cDNAs (for instance, those encoding naturally-occurring variants of PRO or PRO from other species) which have a desired

sequence identity to the native PRO sequence disclosed herein. Optionally, the length of the probes will be about 20 to about 50 bases.

The hybridization probes may be derived from at least partially novel regions of the full length native nucleotide sequence wherein those regions may be determined without undue experimentation or from genomic sequences including promoters, enhancer elements and introns of native sequence PRO. By way of example, a screening method will comprise isolating the coding region of the PRO gene using the known DNA sequence to synthesize a selected probe of about 40 bases. Hybridization probes may be labeled by a variety of labels, including radionucleotides such or enzymatic labels such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems. Labeled probes having a sequence complementary to that of the PRO gene of the present invention can be used to screen libraries of human cDNA, genomic DNA or to determine which members of such libraries the probe hybridizes to. Hybridization techniques are described in further detail in the Examples below.

Any EST sequences disclosed in the present application may similarly be employed as probes, using the methods disclosed herein.

Other useful fragments of the PRO nucleic acids include antisense or sense oligonucleotides comprising a singe-stranded nucleic acid sequence (either RNA or DNA) capable of binding to target PRO (sense) or PRO DNA (antisense) sequences. Antisense or sense oligonucleotides, according to the present invention, comprise a fragment of the coding region of PRO DNA. Such a fragment generally comprises at least about 14 nucleotides, preferably from about 14 to 30 nucleotides. The ability to derive an antisense or a sense oligonucleotide, based upon a cDNA sequence encoding a given protein is described in, for example, Stein and Cohen (Cancer Res. 48 : 2659, 1988) and van der Krol et al. (BioTechniques 6 : 958, 1988).

Binding of antisense or sense oligonucleotides to target nucleic acid sequences results in the formation of duplexes that block transcription or translation of the target sequence by one of several means, including enhanced degradation of the duplexes, premature termination of transcription or translation, or by other means.

The antisense oligonucleotides thus may be used to block expression of PRO proteins. Antisense or sense oligonucleotides further comprise oligonucleotides having modified sugar-phosphodiester backbones (or other sugar linkages, such as those described in WO 91/06629) and wherein such sugar linkages are resistant to endogenous nucleases. Such oligonucleotides with resistant sugar linkages are stable in vivo (i. e., capable of resisting enzymatic degradation) but retain sequence specificity to be able to bind to target nucleotide sequences.

Other examples of sense or antisense oligonucleotides include those oligonucleotides which are covalently linked to organic moieties, such as those described in WO 90/10048, and other moieties that increases affinity of the oligonucleotide for a target nucleic acid sequence, such as poly- (L-lysine). Further still, intercalating agents, such as ellipticine, and alkylating agents or metal complexes may be attached to sense or antisense oligonucleotides to modify binding specificities of the antisense or sense oligonucleotide for the target nucleotide sequence.

Antisense or sense oligonucleotides may be introduced into a cell containing the target nucleic acid sequence by any gene transfer method, including, for example, DNA transfection, electroporation, or by using gene transfer vectors such as Epstein-Barr virus. In a preferred procedure, an antisense or sense oligonucleotide is inserted into a suitable retroviral vector. A cell containing the target nucleic acid sequence is contacted with the recombinant retroviral vector, either in vivo or ex vivo. Suitable

retroviral vectors include, but are not limited to, those derived from the murine retrovirus N2 (a retrovirus derived from M-MuLV), or the double copy vectors designated DCT5A, DCT5B and DCT5C (see WO 90/13641).

Sense or antisense oligonucleotides also may be introduced into a cell containing the target nucleotide sequence by formation of a conjugate with a ligand binding molecule, as described in WO 91/04753. Suitable ligand binding molecules include, but are not limited to, cell surface receptors, growth factors, other or other ligands that bind to cell surface receptors. Preferably, conjugation of the ligand binding molecule does not substantially interfere with the ability of the ligand binding molecule to bind to its corresponding molecule or receptor, or block entry of the sense or antisense oligonucleotide or its conjugated version into the cell.

Alternatively, a sense or an antisense oligonucleotide may be introduced into a cell containing the target nucleic acid sequence by formation of an oligonucleotide-lipid complex, as described in WO 90/10448. The sense or antisense oligonucleotide-lipid complex is preferably dissociated within the cell by an endogenous lipase.

Antisense or sense RNA or DNA molecules are generally at least about 5 bases in length, about 10 bases in length, about 15 bases in length, about 20 bases in length, about 25 bases in length, about 30 bases in length, about 35 bases in length, about 40 bases in length, about 45 bases in length, about 50 bases in length, about 55 bases in length, about 60 bases in length, about 65 bases in length, about 70 bases in length, about 75 bases in length, about 80 bases in length, about 85 bases in length, about 90 bases in length, about 95 bases in length, about 100 bases in length, or more.

The probes may also be employed in PCR techniques to generate a pool of sequences for identification of closely related PRO coding sequences.

Nucleotide sequences encoding a PRO can also be used to construct hybridization probes for mapping the gene which encodes that PRO and for the genetic analysis of individuals with genetic disorders. The nucleotide sequences provided herein may be mapped to a chromosome and specific regions of a chromosome using known techniques, such as in situ hybridization, linkage analysis against known chromosomal markers, and hybridization screening with libraries.

When the coding sequences for PRO encode a protein which binds to another protein (example, where the PRO is a receptor), the PRO can be used in assays to identify the other proteins or molecules involved in the binding interaction. By such methods, inhibitors of the binding interaction can be identified.

Proteins involved in such binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction. Also, the receptor PRO can be used to isolate correlative ligand (s).

Screening assays can be designed to find lead compounds that mimic the biological activity of a native PRO or a receptor for PRO. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates. Small molecules contemplated include synthetic organic or inorganic compounds. The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays and cell based assays, which are well characterized in the art.

Nucleic acids which encode PRO or its modified forms can also be used to generate either transgenic

animals out"animals which, in turn, are useful in the development and screening of therapeutically useful reagents. A transgenic animal (e. g., a mouse or rat) is an animal having cells that contain a transgene, which transgene was introduced into the animal or an ancestor of the animal at a prenatal, e. g., an embryonic stage. A transgene is a DNA which is integrated into the genome of a cell from which a transgenic animal develops. In one embodiment, cDNA encoding PRO can be used to clone genomic DNA encoding PRO in accordance with established techniques and the genomic sequences used to generate transgenic animals that contain cells which express DNA encoding PRO. Methods for generating transgenic animals, particularly animals such as mice or rats, have become conventional in the art and are described, for example, in U. S. Patent Nos.

4, 736, 866 and 4, 870, 009. Typically, particular cells would be targeted for PRO transgene incorporation with tissue-specific enhancers. Transgenic animals that include a copy of a transgene encoding PRO introduced into the germ line of the animal at an embryonic stage can be used to examine the effect of increased expression of DNA encoding PRO. Such animals can be used as tester animals for reagents thought to confer protection from, for example, pathological conditions associated with its overexpression. In accordance with this facet of the invention, an animal is treated with the reagent and a reduced incidence of the pathological condition, compared to untreated animals bearing the transgene, would indicate a potential therapeutic intervention for the pathological condition.

Alternatively, non-human homologues of PRO can be used to construct a out"animal which has a defective or altered gene encoding PRO as a result of homologous recombination between the endogenous gene encoding PRO and altered genomic DNA encoding PRO introduced into an embryonic stem cell of the animal. For example, cDNA encoding PRO can be used to clone genomic DNA encoding PRO in accordance with established techniques. A portion of the genomic DNA encoding PRO can be deleted or replaced with another gene, such as a gene encoding a selectable marker which can be used to monitor integration. Typically, several kilobases of unaltered flanking DNA (both at the 5'and 3'ends) are included in the vector [see e. g., Thomas and Capecchi, Cell, 51 : 503 (1987) for a description of homologous recombination vectors]. The vector is introduced into an embryonic stem cell line (e. g., by electroporation) and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected [see e. g., Li et al., Cell, 69 : 915 (1992)].

The selected cells are then injected into a blastocyst of an animal (e. g., a mouse or rat) to form aggregation chimeras [see e. g., Bradley, in Teratocarcinomas and Embryonic Stem Cells : A Practical Approach, E. J.

Robertson, ed. (IRL, Oxford, 1987), pp. 113-152]. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to create a"knock Progeny harboring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal contain the homologously recombined DNA. Knockout animals can be characterized for instance, for their ability to defend against certain pathological conditions and for their development of pathological conditions due to absence of the PRO polypeptide.

Nucleic acid encoding the PRO polypeptides may also be used in gene therapy. In gene therapy applications, genes are introduced into cells in order to achieve in vivo synthesis of a therapeutically effective genetic product, for example for replacement of a defective gene."Gene therapy"includes both conventional gene therapy where a lasting effect is achieved by a single treatment, and the administration of gene therapeutic agents, which involves the one time or repeated administration of a therapeutically effective DNA or mRNA.

Antisense RNAs and DNAs can be used as therapeutic agents for blocking the expression of certain

genes in vivo.

It has already been shown that short antisense oligonucleotides can be imported into cells where they act as inhibitors, despite their low intracellular concentrations caused by their restricted uptake by the cell membrane.

et Proc. Natl. Acad. Sci. USA 83 : 4143-4146 [1986]). The oligonucleotides can be modified to enhance their uptake, e. g. by substituting their negatively charged phosphodiester groups by uncharged groups.

There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cells in vitro, or in vivo in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into mammalian cells in vitro include the use of liposomes, electroporation, microinjection, cell fusion, DEAE-dextran, the calcium phosphate precipitation method, etc. The currently preferred in vivo gene transfer techniques include transfection with viral (typically retroviral) vectors and viral coat protein-liposome mediated transfection (Dzau et Trends in Biotechnology 205-210 In some situations it is desirable to provide the nucleic acid source with an agent that targets the target cells, such as an antibody specific for a cell surface membrane protein or the target cell, a ligand for a receptor on the target cell, etc. Where liposomes are employed, proteins which bind to a cell surface membrane protein associated with endocytosis may be used for targeting and/or to facilitate uptake, e. g. capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization in cycling, proteins that target intracellular localization and enhance intracellular half-life. The technique of receptor- mediated endocytosis is described, for example, by Wu et al., J. Biol. Chem. 262, 4429-4432 (1987) ; and Wagner et al., Proc. Natl. Acad. Sci. USA 87, 3410-3414 (1990). For review of gene marking and gene therapy protocols see Anderson et Science 256, 808-813 (1992).

The PRO polypeptides described herein may also be employed as molecular weight markers for protein electrophoresis purposes and the isolated nucleic acid sequences may be used for recombinantly expressing those markers.

The nucleic acid molecules encoding the PRO polypeptides or fragments thereof described herein are useful for chromosome identification. In this regard, there exists an ongoing need to identify new chromosome markers, since relatively few chromosome marking reagents, based upon actual sequence data are presently available. Each PRO nucleic acid molecule of the present invention can be used as a chromosome marker.

The PRO polypeptides and nucleic acid molecules of the present invention may also be used diagnostically for tissue typing, wherein the PRO polypeptides of the present invention may be differentially expressed in one tissue as compared to another, preferably in a diseased tissue as compared to a normal tissue of the same tissue type. PRO nucleic acid molecules will find use for generating probes for PCR, Northern analysis, Southern analysis and Western analysis.

The PRO polypeptides described herein may also be employed as therapeutic agents. The PRO polypeptides of the present invention can be formulated according to known methods to prepare pharmaceutically useful compositions, whereby the PRO product hereof is combined in admixture with a pharmaceutically acceptable carrier vehicle. Therapeutic formulations are prepared for storage by mixing the active ingredient having the desired degree of purity with optional physiologically acceptable carriers, excipients or stabilizers (Remington's Pharmaceutical Sciences 16th edition, Osol, A. Ed. (1980)), in the form formulations or aqueous solutions. Acceptable carriers, excipients or stabilizers are to recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate

and other organic acids ; antioxidants including ascorbic acid ; low molecular weight (less than about 10 residues) polypeptides ; proteins, such as serum albumin, gelatin or immunoglobulins ; hydrophilic polymers such as polyvinylpyrrolidone, amino acids such as glycine, glutamin, asparagine, arginine or lysine ; monosaccharides, disaccharides and other carbohydrates including glucose, mannose, or dextrins ; chelating agents such as EDTA ; sugar alcohols such as mannitol or sorbitol ; salt-forming counterions such as sodium ; and/or nonionic surfactants such as TWEEN, or PEG.

The formulations to be used for in vivo administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes, prior to or following lyophilization and reconstitution.

Therapeutic compositions herein generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by a hypodermic injection needle.

The route of administration is in accord with known methods, e. g. injection or infusion by intravenous, intraperitoneal, intracerebral, intramuscular, intraocular, intraarterial or intralesional routes, topical administration, or by sustained release systems.

Dosages and desired drug concentrations of pharmaceutical compositions of the present invention may vary depending on the particular use envisioned. The determination of the appropriate dosage or route of administration is well within the skill of an ordinary physician. Animal experiments provide reliable guidance for the determination of effective doses for human therapy. Interspecies scaling of effective doses can be performed following the principles laid down by Mordenti, J. and Chappell, W."The use of interspecies scaling in toxicokinetics"In Toxicokinetics and New Drug Development, Yacobi et al., Eds., Pergamon Press, New York 1989, pp. 42-96.

When in vivo administration of a PRO polypeptide or agonist or antagonist thereof is employed, normal dosage amounts may vary from about 10 ng/kg to up to 100 mg/kg of mammal body weight or more per day, preferably about to 10 mg/kg/day, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature ; see, for example, U. S. Pat. Nos.

4, 657, 760 ; 5, 206, 344 ; or 5, 225, 212. It is anticipated that different formulations will be effective for different treatment compounds and different disorders, that administration targeting one organ or tissue, for example, may necessitate delivery in a manner different from that to another organ or tissue.

Where sustained-release administration of a PRO polypeptide is desired in a formulation with release characteristics suitable for the treatment of any disease or disorder requiring administration of the PRO polypeptide, microencapsulation of the PRO polypeptide is contemplated. Microencapsulation of recombinant proteins for sustained release has been successfully performed with human growth hormone (rhGH), interferon- and MN et al., Nat. 2 : 795-799 (1996) ; Yasuda, Biomed. Ther., 27 : 1221-1223 (1993) ; Hora et al., 8 : 755-758 (1990) ; Cleland,"Design and Production of Single Immunization Vaccines Using Polylactide Polyglycolide Microsphere Systems,"in Vaccine Design : The Subunit and Adjuvant Approach, Powell and Newman, eds, (Plenum Press : New York, 1995), pp. 439-462 ; WO 97/03692, WO WO 96/07399 ; and U. S. Pat. No. 5, 654, 010.

The sustained-release formulations of these proteins were developed using poly-lactic-coglycolic acid (PLGA) polymer due to its biocompatibility and wide range of biodegradable properties. The degradation products of lactic and glycolic acids, can be cleared quickly within the human body. Moreover, the degradability of this polymer can be adjusted from months to years depending on its

molecular weight and composition. Lewis, "Controlled release of bioactive agents from lactide/glycolide polymer,"in : M. Chasin and R. Langer (Eds.), Biodegradable Polymers as Drug Delivery Systems (Marcel Dekker : New York, 1990), pp. 1-41.

This invention encompasses methods of screening compounds to identify those that mimic the PRO polypeptide (agonists) or prevent the effect of the PRO polypeptide (antagonists). Screening assays for antagonist drug candidates are designed to identify compounds that bind or complex with the PRO polypeptides encoded by the genes identified herein, or otherwise interfere with the interaction of the encoded polypeptides with other cellular proteins. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates.

The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, and cell-based assays, which are well characterized in the art.

All assays for antagonists are common in that they call for contacting the drug candidate with a PRO polypeptide encoded by a nucleic acid identified herein under conditions and for a time sufficient to allow these two components to interact.

In binding assays, the interaction is binding and the complex formed can be isolated or detected in the reaction mixture. In a particular embodiment, the PRO polypeptide encoded by the gene identified herein or the drug candidate is immobilized on a solid phase, e. g., on a microtiter plate, by covalent or non-covalent attachments. Non-covalent attachment generally is accomplished by coating the solid surface with a solution of the PRO polypeptide and drying. Alternatively, an immobilized antibody, e. g., a monoclonal antibody, specific for the PRO polypeptide to be immobilized can be used to anchor it to a solid surface. The assay is performed by adding the non-immobilized component, which may be labeled by a detectable label, to the immobilized component, e. g., the coated surface containing the anchored component. When the reaction is complete, the non- reacted components are removed, e. g., by washing, and complexes anchored on the solid surface are detected.

When the originally non-immobilized component carries a detectable label, the detection of label immobilized on the surface indicates that complexing occurred. Where the originally non-immobilized component does not carry a label, complexing can be detected, for example, by using a labeled antibody specifically binding the immobilized complex.

If the candidate compound interacts with but does not bind to a particular PRO polypeptide encoded by a gene identified herein, its interaction with that polypeptide can be assayed by methods well known for detecting protein-protein interactions. Such assays include traditional approaches, such as, e. g., cross-linking, co- immunoprecipitation, and co-purification through gradients or chromatographic columns. In addition, protein- protein interactions can be monitored by using a yeast-based genetic system described by Fields and co-workers (Fields and Song, Nature 340 : 245-246 (1989) ; Natl. Acad. Sci. USA, 88 : (1991)) as disclosed by Chevray and Nathans, Proc. Natl. Acad. Sci. USA, 89 : 5789-5793 (1991). Many activators, such as yeast GAL4, consist of two physically discrete modular domains, one acting as the DNA-binding domain, the other one functioning as the transcription-activation domain. The yeast expression system described in the foregoing publications (generally referred to as the"two-hybrid system") takes advantage of this property, and employs two hybrid proteins, one in which the target protein is fused to the DNA- binding domain of GAL4, and another, in which candidate activating proteins are fused to the activation domain.

The expression of a GALl-lacZ reporter gene under control of a promoter depends on reconstitution of

GAL4 activity via protein-protein interaction. Colonies containing interacting polypeptides are detected with a chromogenic substrate for A complete kit for identifying protein-protein interactions between two specific proteins using the two-hybrid technique is commercially available from Clontech. This system can also be extended to map protein domains involved in specific protein interactions as well as to pinpoint amino acid residues that are crucial for these interactions.

Compounds that interfere with the interaction of a gene encoding a PRO polypeptide identified herein and other intra-or extracellular components can be tested as follows : usually a reaction mixture is prepared containing the product of the gene and the intra-or extracellular component under conditions and for a time allowing for the interaction and binding of the two products. To test the ability of a candidate compound to inhibit binding, the reaction is run in the absence and in the presence of the test compound. In addition, a placebo may be added to a third reaction mixture, to serve as positive control. The binding (complex formation) between the test compound and the intra-or extracellular component present in the mixture is monitored as described hereinabove. The formation of a complex in the control reaction (s) but not in the reaction mixture containing the test compound indicates that the test compound interferes with the interaction of the test compound and its reaction partner.

To assay for antagonists, the PRO polypeptide may be added to a cell along with the compound to be screened for a particular activity and the ability of the compound to inhibit the activity of interest in the presence of the PRO polypeptide indicates that the compound is an antagonist to the PRO polypeptide. Alternatively, antagonists may be detected by combining the PRO polypeptide and a potential antagonist with membrane-bound PRO polypeptide receptors or recombinant receptors under appropriate conditions for a competitive inhibition assay. The PRO polypeptide can be labeled, such as by radioactivity, such that the number of PRO polypeptide molecules bound to the receptor can be used to determine the effectiveness of the potential antagonist. The gene encoding the receptor can be identified by numerous methods known to those of skill in the art, for example, ligand panning and FACS sorting. Coligan et Current Protocols in Immun., 1 (2) : Chapter 5 (1991).

Preferably, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the PRO polypeptide and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the PRO polypeptide. Transfected cells that are grown on glass slides are exposed to labeled PRO polypeptide. The PRO polypeptide can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase. Following fixation and incubation, the slides are subjected to autoradiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an interactive sub-pooling and re-screening process, eventually yielding a single clone that encodes the putative receptor.

As an alternative approach for receptor identification, labeled PRO polypeptide can be photoaffinity-linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE and exposed to X-ray film. The labeled complex containing the receptor can be excised, resolved into peptide fragments, and subjected to protein The amino acid sequence obtained from micro-sequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the gene encoding the putative receptor.

In another assay for antagonists, mammalian cells or a membrane preparation expressing the receptor would be incubated with labeled PRO polypeptide in the presence of the candidate compound. The ability of the compound to enhance or block this interaction could then be measured.

More specific examples of potential antagonists include an oligonucleotide that binds to the fusions of immunoglobulin with PRO polypeptide, and, in particular, antibodies including, without limitation, poly-and monoclonal antibodies and antibody fragments, single-chain antibodies, anti-idiotypic

antibodies, and chimeric or humanized versions of such antibodies or fragments, as well as human antibodies and antibody fragments.

Alternatively, a potential antagonist may be a closely related protein, for example, a mutated form of the PRO polypeptide that recognizes the receptor but imparts no effect, thereby competitively inhibiting the action of the PRO polypeptide.

Another potential PRO polypeptide antagonist is an antisense RNA or DNA construct prepared using antisense technology, where, e. g., an antisense RNA or DNA molecule acts to block directly the translation of by hybridizing to targeted and preventing protein translation. Antisense technology can be used to control gene expression through triple-helix formation or antisense DNA or RNA, both of which methods are based on binding of a polynucleotide to DNA or RNA. For example, the 5'coding portion of the polynucleotide sequence, which encodes the mature PRO polypeptides herein, is used to design an antisense RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription (triple helix-see Lee et al., Nucl. Acids Res., 6 : 3073 (1979) ; Cooney et Science, 241 : 456 ; 251 : 1360 (1991)), thereby preventing transcription and the production of the PRO polypeptide. The antisense RNA oligonucleotide hybridizes to the in vivo and blocks translation of the molecule into the PRO polypeptide (antisense-Okano, Neurochem., 56 : 560 (1991) ; as Antisense Inhibitors of Gene Expression (CRC Press : 1988).

The oligonucleotides described above can also be delivered to cells such that the antisense RNA or DNA may be expressed in vivo to inhibit production of the PRO polypeptide. When antisense DNA is used, oligodeoxyribonucleotides derived from the translation-initiation site, e. g., between about-10 and + 10 positions of the target gene nucleotide sequence, are preferred.

Potential antagonists include small molecules that bind to the active site, the receptor binding site, or growth factor or other relevant binding site of the PRO polypeptide, thereby blocking the normal biological activity of the PRO polypeptide. Examples of small molecules include, but are not limited to, small peptides or peptide-like molecules, preferably soluble peptides, and synthetic non-peptidyl organic or inorganic compounds.

are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA.

act by sequence-specific hybridization to the complementary target RNA, followed by endonucleolytic cleavage. Specific ribozyme cleavage sites within a potential RNA target can be identified by known techniques.

For further details see, e. g., Rossi, Current Biology, 4 : 469-471 (1994), and PCT publication No. WO 97/33551 (published September 18, 1997).

Nucleic acid molecules in triple-helix formation used to inhibit transcription should be single-stranded and composed of deoxynucleotides. The base composition of these oligonucleotides is designed such that it promotes triple-helix formation via Hoogsteen base-pairing rules, which generally require sizeable stretches of purines or pyrimidines on one strand of a duplex. For further details see, e. g., PCT publication No. WO 97/33551,

These small molecules can be identified by any one or more of the screening assays discussed hereinabove and/or by any other screening techniques well known for those skilled in the art.

Diagnostic and therapeutic uses of the herein disclosed molecules may also be based upon the positive

functional assay hits disclosed and described below.

F. Anti-PRO Antibodies The present invention further provides anti-PRO antibodies. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies.

1. Polyclonal Antibodies The anti-PRO antibodies may comprise polyclonal antibodies. Methods of preparing polyclonal antibodies are known to the skilled artisan. Polyclonal antibodies can be raised in a mammal, for example, by one or more injections of an immunizing agent and, if desired, an adjuvant. Typically, the immunizing agent and/or adjuvant will be injected in the mammal by multiple subcutaneous or intraperitoneal injections. The immunizing agent may include the PRO polypeptide or a fusion protein thereof. It may be useful to conjugate the immunizing agent to a protein known to be immunogenic in the mammal being immunized. Examples of such immunogenic proteins include but are not limited to keyhole limpet hemocyanin, serum albumin, bovine thyroglobulin, and soybean trypsin inhibitor. Examples of adjuvants which may be employed include Freund's complete adjuvant and MPL-TDM adjuvant (monophosphoryl Lipid A, synthetic trehalose dicorynomycolate).

The immunization protocol may be selected by one skilled in the art without undue experimentation.

2. Monoclonal Antibodies The anti-PRO antibodies may, alternatively, be monoclonal antibodies. Monoclonal antibodies may be prepared using hybridoma methods, such as those described by Kohler and Milstein, Nature, 256 : 495 (1975).

In a hybridoma method, a mouse, hamster, or other appropriate host animal, is typically immunized with an immunizing agent to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the immunizing agent. Alternatively, the lymphocytes may be immunized in vitro.

The immunizing agent will typically include the PRO polypeptide or a fusion protein thereof. Generally, either peripheral blood lymphocytes ("PBLs") are used if cells of human origin are desired, or spleen cells or lymph node cells are used if non-human mammalian sources are desired. The lymphocytes are then fused with an immortalized cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell [Goding, Monoclonal Antibodies : Principles and Practice, Academic Press, (1986) pp. 59-103]. Immortalized cell lines are usually transformed mammalian cells, particularly myeloma cells of rodent, bovine and human origin. Usually, rat or mouse myeloma cell lines are employed. The hybridoma cells may be cultured in a suitable culture medium that preferably contains one or more substances that inhibit the growth or survival of the unfused, immortalized cells. For example, if the parental cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine medium"), which substances prevent the growth of HGPRT- deficient cells.

Preferred immortalized cell lines are those that fuse efficiently, support stable high level expression of antibody by the selected antibody-producing cells, and are sensitive to a medium such as HAT medium. More preferred immortalized cell lines are murine myeloma lines, which can be obtained, for instance, from the Salk Institute Cell Distribution Center, San Diego, California and the American Type Culture Collection, Manassas, Virginia. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies [Kozbor, J. Immunol., 133 : 3001 (1984) ; Brodeur et Monoclonal Antibody Marcel Dekker, Inc., New York, (1987) pp. 51-63].

The culture medium in which the hybridoma cells are cultured can then be assayed for the presence of monoclonal antibodies directed against PRO. Preferably, the binding specificity of monoclonal antibodies produced by the hybridoma cells is determined by immunoprecipitation or by an in vitro

binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunoabsorbent assay (ELISA). Such techniques and assays are known in the art. The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis of Munson and Pollard, Anal. Biochem., : 220 (1980).

After the desired hybridoma cells are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods [Goding, supra. Suitable culture media for this purpose include, for example, Modified Eagle's Medium and RPMI-1640 medium. Alternatively, the hybridoma cells may be grown in vivo as ascites in a mammal.

The monoclonal antibodies secreted by the subclones may be isolated or purified from the culture medium or ascites fluid by conventional immunoglobulin purification procedures such as, for example, protein A- Sepharose, hydroxylapatite chromatography, gel electrophoresis, dialysis, or affinity chromatography.

The monoclonal antibodies may also be made by recombinant DNA methods, such as those described in U. S. Patent No. 4, 816, 567. DNA encoding the monoclonal antibodies of the invention can be readily isolated and sequenced using conventional procedures (e. g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the heavy and light chains of murine antibodies). The hybridoma cells of the invention serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as simian COS cells, Chinese hamster ovary (CHO) cells, or myeloma cells that do not otherwise produce immunoglobulin protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. The DNA also may be modified, for example, by substituting the coding sequence for human heavy and light chain constant domains in place of the homologous murine sequences [U. S.

Patent No. 4, 816, 567 ; Morrison et al., supral or by covalently joining to the immunoglobulin coding sequence all or part of the coding sequence for a non-immunoglobulin polypeptide. Such a non-immunoglobulin polypeptide can be substituted for the constant domains of an antibody of the invention, or can be substituted for the variable domains of one antigen-combining site of an antibody of the invention to create a chimeric bivalent antibody.

The antibodies may be monovalent antibodies. Methods for preparing monovalent antibodies are well known in the art. For example, one method involves recombinant expression of immunoglobulin light chain and modified heavy chain. The heavy chain is truncated generally at any point in the Fc region so as to prevent heavy chain crosslinking. Alternatively, the relevant cysteine residues are substituted with another amino acid residue or are deleted so as to prevent crosslinking.

In vitro methods are also suitable for preparing monovalent antibodies. Digestion of antibodies to produce fragments thereof, particularly, Fab fragments, can be accomplished using routine techniques known in the art.

3. Human and Humanized Antibodies The anti-PRO antibodies of the invention may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e. g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F (ab') 2 or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin.

Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a

non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region typically that of a human immunoglobulin [Jones et al., Nature, 321 : 522-525 (1986) ; Riechmann et al., Nature, 332 : 323-329 ; and Presta, Curr. Op. Struct. 2 : 593-596

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non- human amino acid residues are often referred to as"import"residues, which are typically taken from an"import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers [Jones et al., Nature, 321 : 522-525 (1986) ; Riechmann et Nature, 332 : 323-327 (1988) ; Verhoeyen et al., Science, 239 : 1534-1536 (1988)], by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such"humanized"antibodies are chimeric antibodies (U. S. Patent No.

4, 816, 567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some residues are substituted by residues from analogous sites in rodent antibodies.

Human antibodies can also be produced using various techniques known in the art, including phage display libraries [Hoogenboom and Winter, J. Mol. 227 : 381 (1991) ; Marks et al., J. Mol. 222 : 581 (1991)]. The techniques of Cole et al. and Boerner et al. are also available for the preparation of human monoclonal antibodies (Cole et al., Monoclonal Antibodies and Cancer Therapy, Alan R. Liss, p. 77 (1985) and Boerner et al., J. Immunol., 86-95 (1991)]. Similarly, human antibodies can be made by introducing of human immunoglobulin loci into transgenic animals, e. g., mice in which the endogenous immunoglobulin genes have been partially or completely inactivated. Upon challenge, human antibody production is observed, which closely resembles that seen in humans in all respects, including gene rearrangement, assembly, and antibody repertoire. This approach is described, for example, in U. S. Patent Nos. 5, 545, 807 ; 5, 545, 806 ; 5, 569, 825 ; 5, 625, 126 ; 5, 633, 425 ; 5, 661, 016, and in the following scientific publications : Marks 779-783 (1992) ; Lonberg Nature 368 856-859 (1994) ; Morrison, Nature 812-13 (1994) ; Fishwild et Nature Biotechnology 845-51 (1996) ; Neuberger, Nature Biotechnology 826 (1996) ; Lonberg and Huszar, Intern. Rev. Immunol. 13 65-93 (1995).

The antibodies may also be affinity matured using known selection and/or mutagenesis methods as described above. Preferred affinity matured antibodies have an affinity which is five times, more preferably 10 times, even more preferably 20 or 30 times greater than the starting antibody (generally murine, humanized or human) from which the matured antibody is prepared.

4. Bispecific Antibodies Bispecific antibodies are monoclonal, preferably human or humanized, antibodies that have binding specificities for at least two different antigens. In the present case, one of the binding specificities is for the PRO, the other one is for any other antigen, and preferably for a cell-surface protein or receptor or receptor subunit.

Methods for making bispecific antibodies are known in the art. Traditionally, the recombinant production of bispecific antibodies is based on the co-expression of two immunoglobulin pairs, where

the two heavy chains have different specificities [Milstein and Cuello, Nature, 305 : 537-539 (1983)]. Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of ten different antibody molecules, of which only one has the correct bispecific structure. The purification of the correct molecule is usually accomplished by affinity chromatography steps. Similar procedures are disclosed in WO 93/08829, published 13 May 1993, and in et al., EMBO J., 10 : 3655-3659 (1991).

Antibody variable domains with the desired binding specificities (antibody-antigen combining sites) can be fused to immunoglobulin constant domain sequences. The fusion preferably is with an immunoglobulin heavy- chain constant domain, comprising at least part of the hinge, CH2, and CH3 regions. It is preferred to have the first heavy-chain constant region (CH1) containing the site necessary for light-chain binding present in at least one of the fusions. DNAs encoding the immunoglobulin heavy-chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are into a suitable host organism.

For further details of generating bispecific antibodies see, for example, Suresh et Methods in : 210 (1986).

According to another approach described in WO 96/27011, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the CH3 region of an antibody constant domain.

In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e. g. tyrosine or tryptophan). Compensatory"cavities"of identical or similar size to the large side chain (s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e. g. alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e. g. F (ab') 2 bispecific antibodies). Techniques for generating bispecific antibodies from antibody fragments have been described in the literature. For example, bispecific antibodies can be prepared can be prepared using chemical linkage. Brennan et Science 229 : 81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate F (ab') 2 fragments. These fragments are reduced in the presence of the dithiol complexing agent sodium arsenite to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with and is mixed with an amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

Fab'fragments may be directly recovered from E. coli and chemically coupled to form bispecific antibodies. Shalaby et J. Exp. Med. 175 : 217-225 (1992) describe the production of a fully humanized bispecific antibody F molecule. Each Fab'fragment was separately secreted from E. coli and subjected to directed chemical coupling in vitro to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

Various technique for making and isolating bispecific antibody fragments directly from recombinant cell

culture have also been described. For example, bispecific antibodies have been produced using leucine zippers.

Kostelny et J. Immunol. 148 (5) : 1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab'portions of two different antibodies by gene fusion. The antibody were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody The"diabody"technology described by Hollinger et Proc. Natl. Acad. Sci. USA 90 : 6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a heavy-chain variable domain connected to a light-chain variable domain by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the VH and VL domains of one fragment are forced to pair with the complementary VL and VH domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain (sFv) dimers has also been reported. See, Gruber et J. Immunol. 152 : 5368 (1994).

Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared.

Tutt et J. Immunol. 147 : 60 (1991).

Exemplary bispecific antibodies may bind to two different epitopes on a given PRO polypeptide herein.

Alternatively, an anti-PRO polypeptide arm may be combined with an arm which binds to a triggering molecule on a leukocyte such as a T-cell receptor molecule (e. g. CD2, CD28, or B7), or Fc receptors for IgG (FcyR), such as (CD64), FcyRII (CD32) and FcyRIII (CD16) so as to focus cellular defense mechanisms to the cell expressing the particular PRO polypeptide. Bispecific antibodies may also be used to localize cytotoxic agents to cells which express a particular PRO polypeptide. These antibodies possess a PRO-binding arm and an arm which binds a cytotoxic agent or a radionuclide chelator, such as EOTUBE, DPTA, DOTA, or TETA.

Another bispecific antibody of interest binds the PRO polypeptide and further binds tissue factor (TF).

5. Antibodies Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells [U. S. Patent No. 4, 676, 980], and for treatment of HIV infection [WO 91/00360 ; WO 92/200373 ; EP 03089]. It is contemplated that the antibodies may be prepared in vitro using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins may be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptobutyrimidate and those disclosed, for example, in U. S. Patent No. 4, 676,

6. Effector Function Engineering It may be desirable to modify the antibody of the invention with respect to effector function, so as to enhance, e. g., the effectiveness of the antibody in treating cancer. For example, cysteine residue (s) may be introduced into the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated may have improved internalization capability and/or increased complement- mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron et J. Exp Med., 176 : 1191-1195 (1992) J. Immunol., : 2918-2922 (1992). Homodimeric antibodies with enhanced anti- tumor activity may also be prepared using cross-linkers as described in Wolff et al. Cancer Research, 53 : 2560-2565 (1993). Alternatively, an

antibody can be engineered that has dual Fc regions and may thereby have enhanced complement lysis and ADCC capabilities. See Stevenson et Anti-Cancer Drug Design.

3 : 219-230 (1989).

7. The invention also pertains to irnmunoconjugates comprising an antibody conjugated to a cytotoxic agent such as a chemotherapeutic agent, toxin (e. g., an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (i. e., a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above.

Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from Pseudomonas ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, proteins, dianthin proteins, Phytolaca americana proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, enomycin, and the tricothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include and

Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutareldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis- (p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2, 6-diisocyanate), and bis- active fluorine compounds (such as 5-difluoro-2, 4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et Science, 238 : 1098 (1987). methyldiethylene acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See

In another embodiment, the antibody may be conjugated to a"receptor" (such streptavidin) for utilization in tumor pretargeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a"ligand" (e. g., avidin) that is conjugated to a cytotoxic agent (e. g., a radionucleotide).

8. Immunoliposomes The antibodies disclosed herein may also be formulated as immunoliposomes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein et Proc. Natl. Acad. Sci.

USA, : 3688 ; Hwang et Proc. Natl Acad. Sci. USA, 77 : 4030 (1980) ; and U. S. Pat. Nos.

4, 045 544, 545. Liposomes with enhanced circulation time are S. Patent No. 5, 013, 556.

Particularly useful liposomes can be generated by the reverse-phase evaporation method with a lipid composition comprising cholesterol, and PEG-derivatized phosphatidylethanolamine (PEG- PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter.

Fab'fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin et al., J. Biol. 257 : 286-288 (1982) via a disulfide-interchange reaction. A chemotherapeutic agent (such as Doxorubicin) is optionally contained within the liposome. See 81 (19) : 1484 (1989).

9. Pharmaceutical Compositions of Antibodies Antibodies specifically binding a PRO polypeptide identified herein, as well as other molecules identified by the screening assays disclosed hereinbefore, can be administered for the treatment of various disorders in the form of pharmaceutical compositions.

If the PRO polypeptide is intracellular and whole antibodies are used as inhibitors, internalizing antibodies are preferred. However, lipofections or liposomes can also be used to deliver the antibody, or an antibody fragment, into cells. Where antibody fragments are used, the smallest inhibitory fragment that specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable- region sequences of an antibody, peptide molecules can be designed that retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology. See, e. g., Marasco et Proc. Natl. Acad. Sci. USA, 90 : 7889-7893 (1993). The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Alternatively, or in addition, the composition may comprise an agent that enhances its function, such as, for example, a cytotoxic agent, cytokine, chemotherapeutic agent, or growth-inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly- (methylmethacylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, nano-particles, or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences, supra.

The formulations to be used for in vivo administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semipermeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e. g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly (2-hydroxyethyl-methacrylate), or poly (vinylalcohol)), polylactides (U. S.

Pat. No. 3, 773, 919), copolymers of L-glutamic acid and ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT (injectable microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D- (-)-3-hydroxybutyric acid.

While polymers such as ethylene-vinyl acetate and lactic acid-glycolic acid enable release of molecules for over 100 days, certain hydrogels release proteins for shorter time periods. When encapsulated antibodies remain in the body for a long time, they may denature or aggregate as a result of exposure to moisture at resulting in a loss of biological activity and possible changes in immunogenicity. Rational strategies can be devised for stabilization depending on the mechanism involved. For example, if the aggregation mechanism is discovered to be intermolecular S-S bond formation through interchange, stabilization may be achieved by modifying sulfhydryl residues, from acidic solutions, controlling moisture content, using appropriate additives, and developing specific polymer matrix compositions.

G. Uses for anti-PRO Antibodies The anti-PRO antibodies of the invention have various utilities. For example, anti-PRO antibodies may be used in diagnostic assays for PRO, e. g., detecting its expression (and in some cases, differential expression) in specific cells, tissues, or serum. Various diagnostic assay

techniques known in the art may be used, such as competitive binding assays, direct or indirect sandwich assays and immunoprecipitation assays conducted in either heterogeneous or homogeneous phases [Zola, Monoclonal Antibodies : A Manual of Techniques. CRC Press, Inc.

(1987) pp. 147-158]. The antibodies used in the diagnostic assays can be labeled with a detectable moiety. The detectable moiety should be capable of producing, either directly or indirectly, a detectable signal. For example, the detectable moiety may be a radioisotope, such a fluorescent or chemiluminescent compound, such as fluorescein isothiocyanate, rhodamine, or luciferin, or an enzyme, such as alkaline phosphatase, beta-galactosidase or horseradish peroxidase. Any method known in the art for conjugating the antibody to the detectable moiety may be employed, including those methods described by Hunter et al., Nature, 144 : 945 (1962) ; David et Biochemistry, : 1014 (1974) ; Pain et al., J. Immunol. 40 : 219 ; and Nygren, J. Histochem. and 30 : 407 (1982).

Anti-PRO antibodies also are useful for the affinity purification of PRO from recombinant cell culture or natural sources. In this process, the antibodies against PRO are immobilized on a suitable support, such a Sephadex resin or filter paper, using methods well known in the art. The immobilized antibody then is contacted with a sample containing the PRO to be purified, and thereafter the support is washed with a suitable solvent that will remove substantially all the material in the sample except the PRO, which is bound to the immobilized antibody. Finally, the support is washed with another suitable solvent that will release the PRO from the antibody.

The following examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

EXAMPLES Commercially available reagents referred to in the examples were used according to manufacturer's instructions unless otherwise indicated. The source of those cells identified in the following examples, and throughout the specification, by ATCC accession numbers is the American Type Culture Collection, Manassas, VA.

EXAMPLE 1 : Extracellular Domain Screening to Identify Novel Polypeptides and cDNA Encoding Therefor The extracellular domain (ECD) sequences (including the secretion signal sequence, if any) from about 950 known secreted proteins from the Swiss-Prot public database were used to search EST databases. The EST databases included public databases (e. g., Dayhoff, GenBank), and proprietary databases (e. g. Incyte Pharmaceuticals, Palo Alto, CA). The search was performed using the computer program BLAST or BLAST-2 (Altschul et Methods in 266 : 460-480 (1996)) as a comparison of the protein sequences to a 6 frame translation of the EST sequences. Those comparisons with a BLAST score of 70 (or in some cases 90) or greater that did not encode known proteins were clustered and assembled into consensus DNA sequences with the program"phrap" (Phil Green, University of Washington, Seattle, WA).

Using this extracellular domain homology screen, consensus DNA sequences were assembled relative to the other identified EST sequences using phrap. In addition, the consensus DNA sequences obtained were often (but not always) extended using repeated cycles of BLAST or BLAST-2 and phrap to extend the consensus sequence as far as possible using the sources of EST sequences discussed above.

Based upon the consensus sequences obtained as described above, oligonucleotides were then synthesized and used to identify by PCR a cDNA library that contained the sequence of interest and for

use as probes to isolate a clone of the full-length coding sequence for a PRO polypeptide. Forward and reverse PCR primers generally range from 20 to 30 nucleotides and are often designed to give a PCR product of about 100-1000 bp in length. The probe sequences are typically 40-55 bp in length. In some cases, additional oligonucleotides are synthesized when the consensus sequence is greater than about In order to screen several libraries for a full-length clone, DNA from the libraries was screened by PCR amplification, as per Ausubel et Current Protocols in Molecular Biology, with the PCR primer pair. A positive library was then used to isolate clones encoding the gene of interest using the probe oligonucleotide and one of the primer pairs.

The cDNA libraries used to isolate the cDNA clones were constructed by standard methods using commercially available reagents such as those from Invitrogen, San Diego, CA. The cDNA was primed with oligo dT containing a NotI site, linked with blunt to SalI adaptors, cleaved with NotI, sized appropriately by gel electrophoresis, and cloned in a defined orientation into a suitable cloning vector (such as pRKB or ; pRK5B is a precursor of pRK5D that does not contain the SfiI site ; see, Holmes et Science, 253 : 1278-1280 (1991)) in the unique XhoI and NotI sites.

EXAMPLE 2 : Isolation of cDNA clones by Screening Preparation of oligo dT primed cDNA library was isolated from a human tissue of interest using reagents and protocols from Invitrogen, San Diego, CA (Fast Track 2). This RNA was used to generate an oligo dT primed cDNA library in the vector pRK5D using reagents and protocols from Life Technologies, Gaithersburg, MD (Super Script Plasmid System).

In this procedure, the double stranded cDNA was sized to greater than 1000 bp and the linkered cDNA was cloned into XhoI/NotI cleaved vector. pRK5D is a cloning vector that has an sp6 transcription initiation site followed by an SfiI restriction enzyme site preceding the XhoI/NotI cDNA cloning sites.

2. Preparation of random primed cDNA library A secondary cDNA library was generated in order to preferentially represent the 5'ends of the primary cDNA clones. Sp6 RNA was generated from the primary library (described above), and this RNA was used to generate a random primed cDNA library in the vector pSST-AMY. using reagents and protocols from Life Technologies (Super Script Plasmid System, referenced above). In this procedure the double stranded cDNA was sized to 500-1000 bp, linkered with blunt to NotI adaptors, cleaved with SfiI, and cloned into cleaved vector. pSST-AMY. is a cloning vector that has a yeast alcohol dehydrogenase promoter preceding the cDNA cloning sites and the mouse amylase sequence (the mature sequence without the secretion signal) followed by the yeast alcohol dehydrogenase terminator, after the cloning sites. Thus, cDNAs cloned into this vector that are fused in frame with amylase sequence will lead to the secretion of amylase from appropriately transfected yeast colonies.

3. Transformation and Detection DNA from the library described in paragraph 2 above was chilled on ice to which was added DH10B bacteria (Life Technologies, 20 ml). The bacteria and vector mixture was then electroporated as recommended by the manufacturer. Subsequently, SOC media (Life Technologies, 1 ml) was added and the mixture was incubated at for 30 minutes. The transformants were then plated onto 20 standard 150 mm LB plates containing ampicillin and incubated for 16 hours Positive colonies were scraped off the plates and the DNA was isolated from the bacterial pellet using standard protocols, e. g. CsCl- gradient. The purified DNA was then carried on to the yeast protocols below.

The yeast methods were divided into three categories : (1) Transformation of yeast with the plasmid/cDNA combined vector ; (2) Detection and isolation of yeast clones secreting amylase ; and (3) PCR amplification of the insert directly from the yeast colony and purification of the DNA for sequencing and further analysis.

The yeast strain used was HD56-5A (ATCC-90785). This strain has the following genotype : MAT alpha, ura3-52, leu2-3, leu2-112, his3-15, MAL+, Preferably, yeast mutants can be employed that have deficient post-translational pathways. Such mutants may have translocation deficient alleles with truncated sec71 being most preferred. Alternatively, antagonists (including antisense nucleotides and/or ligands) which interfere with the normal operation of these genes, other proteins implicated in this post translation pathway (e. g., SEC61p, SEC72p, SEC62p, SEC63p, TDJlp or SSAlp-4p) or the complex formation of these proteins may also be preferably employed in combination with the amylase-expressing yeast.

Transformation was performed based on the protocol outlined by Gietz et Nucl. Acid. Res., 20 : 1425 (1992). Transformed cells were then inoculated from agar into YEPD complex media broth (100 ml) and grown overnight at The YEPD broth was prepared as described in Kaiser et Methods in Yeast Genetics, Cold Spring Harbor Press, Cold Spring Harbor, NY, p. 207 (1994). The overnight culture was then diluted to about 2 x 106 cells/ml (approx. into fresh YEPD broth (500 ml) and regrown to 1 x (approx.

The cells were then harvested and prepared for transformation by transfer into GS3 rotor bottles in a Sorval GS3 rotor at 5, 000 rpm for 5 minutes, the supernatant discarded, and then resuspended into sterile water, and centrifuged again in 50 ml falcon tubes at 3, 500 rpm in a GS-6KR centrifuge. The supernatant was discarded and the cells were subsequently washed with LiAc/TE (10 ml, 10 mM 1 mM EDTA pH 7. 5, 100 mM and resuspended into LiAc/TE (2. 5

Transformation took place by mixing the prepared cells with freshly denatured single stranded salmon testes DNA (Lofstrand Labs, Gaithersburg, MD) and transforming DNA vol. < in tubes. The mixture was mixed briefly by vortexing, then PEG/TE polyethylene glycol-4000, 10 mM mM EDTA, 100 mM pH 7. 5) was added. This mixture was gently mixed and incubated at while agitating for 30 minutes. The cells were then heat shocked at for 15 minutes, and the reaction vessel centrifuged in a at 12, 000 rpm for 5-10 seconds, decanted and resuspended into TE (500 10 mM 1 mM EDTA pH 7. 5) followed by recentrifugation. The cells were then diluted into TE (1 ml) and aliquots (200 were spread onto the selective media previously prepared in 150 mm growth plates (VWR).

Alternatively, instead of multiple small reactions, the transformation was performed using a single, large scale reaction, wherein reagent amounts were scaled up accordingly.

The selective media used was a synthetic complete dextrose agar lacking uracil (SCD-Ura) prepared as described in Kaiser et Methods in Yeast Genetics, Cold Spring Harbor Press, Cold Spring Harbor, NY, p.

208-210 (1994). Transformants were grown at for 2-3 days.

The detection of colonies secreting amylase was performed by including red starch in the selective growth media. Starch was coupled to the red dye (Reactive Red-120, Sigma) as per the procedure described by Biely et Anal. Biochem., 172 : 176-179 (1988). The coupled starch was incorporated into the SCD-Ura agar plates at a final concentration of 0. 15 % (w/v), and was buffered with potassium phosphate to a pH of 7. 0 (50-100 mM final concentration).

The positive colonies were picked and streaked across fresh selective media (onto 150 mm plates) in order to obtain well isolated and identifiable single colonies. Well isolated single colonies positive for amylase secretion were detected by direct incorporation of red starch into buffered SCD-Ura agar. Positive colonies were determined by their ability to break down starch resulting in a clear halo around the positive colony visualized directly.

4. Isolation of DNA by PCR Amplification When a positive colony was isolated, a portion of it was picked by a toothpick and diluted into sterile water in a 96 well plate. At this time, the positive colonies were either frozen and stored for subsequent analysis or immediately amplified. An aliquot of cells (5 was used as a template for the PCR reaction in a volume containing : 0. (Clontech, Palo Alto, CA) ; 4. 10 mM dNTP's ; 2. Kentaq buffer (Clontech) ; 0. forward oligo 1 ; 0. 25 reverse oligo 2 ; 12. distilled water. The sequence of the forward oligonucleotide 1 was : 5'-TGTAAAACGACGGCCAGTTAAATAGACCTGCAATTATTAATCT-3' (SEQ ID NO : 611) The sequence of reverse oligonucleotide 2 was : 5'-CAGGAAACAGCTATGACCACCTGCACACCTGCAAATCCATT-3' (SEQ ID NO : 612) PCR was then performed as follows : a. Denature 5 minutes b. 3 cycles of : Denature 30 seconds Anneal 30 seconds Extend 60 seconds 3 cycles of : Denature 30 seconds Anneal 30 seconds Extend 60 seconds d. 25 cycles of : Denature 30 seconds Anneal 30 seconds Extend 60 seconds e. Hold The underlined regions of the oligonucleotides annealed to the ADH promoter region and the amylase region, respectively, and amplified a 307 bp region from vector pSST-AMY. when no insert was present.

Typically, the first 18 nucleotides of the 5'end of these oligonucleotides contained annealing sites for the sequencing primers. Thus, the total product of the PCR reaction from an empty vector was 343 bp. However, signal sequence-fused cDNA resulted in considerably longer nucleotide sequences.

Following the PCR, an aliquot of the reaction (5 was examined by agarose gel electrophoresis in a gel using a Tris-Borate-EDTA (TBE) buffering system as described by Sambrook et supra.

Clones resulting in a single strong PCR product larger than 400 bp were further analyzed by DNA sequencing after purification with a 96 Qiaquick PCR clean-up column (Qiagen Inc., Chatsworth, CA).

EXAMPLE 3 : Isolation of cDNA Clones Using Signal Algorithm Analysis Various polypeptide-encoding nucleic acid sequences were identified by applying a proprietary signal sequence finding algorithm developed by Genentech, Inc. (South San Francisco, CA) upon ESTs as well as clustered and assembled EST fragments from public (e. g., GenBank) and/or private Incyte Pharmaceuticals, Inc., Palo Alto, CA) databases. The signal sequence algorithm computes a secretion signal score based on the character of the DNA nucleotides surrounding the first and optionally the second methionine codon (s) (ATG) at the 5'-end of the sequence or sequence fragment under consideration. The nucleotides following the first ATG must code for at least 35 unambiguous amino acids without any stop codons. If the first ATG has the required amino acids, the second is not examined. If neither meets the requirement, the candidate sequence is not scored. In order to determine whether the EST sequence contains an authentic signal sequence, the DNA and corresponding amino acid sequences surrounding the ATG codon are scored using a set of seven sensors (evaluation parameters) known to be associated with secretion signals. Use of this algorithm resulted in the identification of numerous polypeptide-encoding nucleic acid sequences.

EXAMPLE 4 : Isolation of cDNA clones Encoding Human PRO Polypeptides Using the techniques described in Examples 1 to 3 above, numerous full-length cDNA clones were identified as encoding PRO polypeptides as disclosed herein. These cDNAs were then deposited under the terms of the Budapest Treaty with the American Type Culture Collection, 10801 University Blvd., Manassas, VA 20110-2209, USA (ATCC) as shown in Table 7 below.

Table 7 No. Deposit Date 1998 DNA23318-1211 209787 April 21, 1998 DNA23322-1393 203400 October 27, 1998 DNA23334-1392 209918 June 2, 1998 DNA26843-1389 203099 August 4, 1998 DNA 2, 1998 DNA30867-1335 209807 April 28, 1998 DNA33470-1175 209398 October 17, 1997 10, 1997 DNA35557-1137 209255 September 16, 1997 DNA35599-1168 209373 October 16, 1997 DNA35668-1171 209371 October 16, 1997 DNA36992-1168 209382 October 16, 1997 DNA39423-

1182 209387 October 17, 1997 DNA39427-1179 209395 October 17, 1997 DNA39510-1181 209392 October 17, 1997 10, 1997 DNA39975-1210 209783 April 21, 1998 10, 1997 DNA39979-1213 209789 April 21, 1998 5, 1998 DNA40603-1232 209486 November 21, 1997 DNA40604-1187 209394 October 17, 1997 DNA40625-1189 209788 April 21, 1998 DNA41225-1217 209491 November 21, 1997 DNA41379-1236 209488 November 21, 7 1998 DNA44161-1434 209907 May 27, 1998 DNA44179-1362 209851 May 6, 1998 DNA44192-1246 209531 December 10, 1997 DNA44694-1500 203114 August 11, 1998 DNA45234-1277 209654 March 5, 1998 DNA45409-2511 203579 January 12, 1999 DNA45415-1318 209810 April 28, 1998 1998 DNA45493-1349 209805 April 28, 1998 Table 7 No. Deposit Date DNA46776-1284 209721 March 31, 1998 11, 1998 DNA48306-1291 209911 May 27, 1998 1998 DNA48334-1435 209924 June 2, 1998 DNA49141-1431 203003 June 23, 1998 DNA49624-1279 209655 March 5, 1998 DNA49647-1398 209919 June 2, 1998 DNA49819-1439 209931 June 2, 1998 DNA50911-1288 209714 March 31, 1998 DNA50914-1289 209722 March 31, 1998 6, 1998 1998 14, 1998 DNA53906-1368 209747 April 7, 1998 14, 1998 DNA53913-1490 203162 August 25, 1998 DNA53977-1371 209862 May 14, 1998 DNA53978-1443 209983 June 16, 1998 2, 1998 DNA54002-1367 209754 April 7, 1998 DNA56050-1455 203011 June 23, 1998 DNA56052-1454 203026 June 23, 1998 DNA56107-1415 203405 October 27, 1998 DNA56110-1437 203113 August 11, 1998 DNA56406-1704 203478 November 17, 1998 DNA56409-1377 209882 May 20, 1998 2, 1998 DNA56436-1448 209902 May 27, 1998 DNA56529-1647 203293 September 29, 1998 DNA56855-1447 203004 June 23, 1998 DNA56859-1445 203019 June 23, DNA56860-1510 209952 June 9, 1998 DNA56865-1491 203022 June 23, 1998 Table 7 Material ATCC Dep. No. Deposit Date DNA56868-1478 203024 June 23, 1998 DNA56869-1545 203161 August 25, 1998 DNA56870-1492 209925 June 2, DNA57039-1402 209777 April 14, 1998 DNA57253-1382 209867 May 14, 1998 DNA57254-1477 203289 September 29, 1998 23, 1998 DNA57704-1452 209953 June 9, 1998 1, 1998 1, 1998 23, DNA58723-1588 203133 August 18, 1998 DNA58727-1474 203171 September 1, 1998 DNA58730-1607 203221 September 15, 1998 DNA58732-1650 203290 September 29, 1998 1998 DNA58743-1609 203154 August 25, 1998 DNA58747-1384 209868 May 14, 1998 DNA58828-1519 203172 September 1, 1998 DNA58846-1409 209957 June 9, 1998 DNA58848-1472 209955 June 9, 1998 DNA58849-1494 209958 June 9, 1998 DNA58850-1495 209956 June 9, DNA58852-1637 203271 September 22, 1998 23, 1998 DNA58855-1422 203018 June 23, 1998 9, 1998 DNA59212-1627 203245 September 9, 1998 DNA59213-1487 209959 June 9, 1998 DNA59219-1613 203220 September 15, 1998 4, 1998 DNA59602-1436 203051 July 1, 1998 DNA59603-1419 209944 June 9, 1998 DNA59605-1418 203005 June 23, 1998 DNA59607-1497 209946 June 9, 1998 DNA59610-1556 209990 June 16, 1998 Table 7 Material ATCC Dep. No. Deposit Date DNA59612-1466 209947 June 9, 1998 DNA59613-1417 203007 June 23, 1998 DNA59616-1465 209991 June 16, 1998 DNA59619-1464 203041 July 1, 1998 16, 17, 1998 DNA59827-1426 203089 August 4, 1998 25, 1998 DNA59837-2545 203658 February 9, 1999 DNA59844-2542 203650 February 9, 1999 16, DNA59854-1459 209974 June 16, 1998 DNA59855-1485 209987 June 16, 1, 1998 1, 1998 DNA60608-1577 203126 August 18, 1998 DNA60619-1482 209993 June 16, 1998 DNA60625-1507 209975 June 16, 1998 DNA60629-1481 209979 June 16, 1998 DNA60740-1615 203456 November 3, 1998 DNA61608-1606 203239 September 9, 1998 DNA61755-1554 203112 August 11, 1998 DNA62809-1531 203237 September 9, DNA62812-1594 203248 September 9, 1998 DNA62813-2544 203655 February 9, 1999 DNA62845-1684 203361 October 20, 1998 17, 1998 18, 1998 9, 9, DNA64902-1667 203317 October 6, 1998 15, 1998 15, 1998 DNA65413-1534 203234 September 15, 1998 DNA65423-1595 203227 September 15, 1998 Table 7 No. Deposit Date 6, 1998 DNA66308-1537 203159 August 25, 1998 15, 1998 DNA66512-1564 203218 September 15, 1998 DNA66519-1535 203236 September 15, 1998 203225 September 15, 1998 DNA66658-1584 203229 September 15, 1998 DNA66660-1585 203279 September 22, 1998 DNA66669-1597 203272 September 22, 1998 DNA66674-1599 203281 September 22, 1998 DNA68836-1656 203455 November 3, 1998 DNA68862-2546 203652 February 9, 1999 DNA68866-1644 203283 September 22, 1998 DNA68869-1610 203164 August 25, 1998 DNA68871-1638 203280 September 22, 1998 DNA68879-1631 203274 September 22, DNA68880-1676 203319 October 6, 1998 DNA68882-1677 203318 October 6, 1998 DNA68883-1691 203535 December 15, 1998 DNA68885-

1678 203311 October 6, 1998 DNA71180-1655 203403 October 27, 1998 DNA71184-1634 203266 September 22, 1998 DNA71213-1659 203401 October 27, 1998 DNA71234-1651 203402 October 27, 1998 DNA71269-1621 203284 September 22, 1998 DNA71277-1636 203285 September 22, 1998 DNA71286-1687 203357 October 20, 1998 DNA71883-1660 203475 November 17, 1998 DNA73401-1633 203273 September 22, 1998 DNA73492-1671 203324 October 6, 1998 DNA73730-1679 203320 October 6, 1998 20, 1998 1998 6, 1998 DNA73746-1654 203411 October 27, 1998 DNA73760-1672 203314 October 6, Table 7 No. Deposit Date DNA76393-1664 203323 October 6, 1998 DNA76398-1699 203474 November 17, 1998 DNA76399-1700 203472 November 17, DNA76522-2500 203469 November 17, DNA76533-1689 203410 October 27, 1998 DNA77303-2502 203479 November 17, 1998 15, DNA77648-1688 203408 October 27, 1998 15, 1998 15, 1998 15, 1998 22, 1998 9, 1999 20, 1999 8, 1999 DNA23336-2861 PTA-1673 April 11, 2000 2, 1998 DNA30871-1157 209380 October 16, 1997 DNA32279-1131 209259 September 16, 1997 DNA33206-1165 209372 October 16, 1997 DNA35673-1201 209418 October 28, 1997 DNA47361-1154-2 209431 November 7, 1997 DNA52594-1270 209679 March 17, 1998 DNA55800-1263 209680 March 17, 1998 29, 1998 1998 DNA57037-1444 209903 May 27, 1998 DNA57695-1340 203006 June 23, 1998 DNA57834-1339 209954 June 9, 1998 DNA57841-1522 203458 November 3, 1998 DNA59493-1420 203050 July 1, 1998 DNA59586-1520 203288 September 29, 1998 DNA59608-2577 203870 March 23, 1999 DNA59849-1504 209986 June 16, 1998 Table 7 No. Deposit Date 15, 1998 DNA62377-1381-1 203552 December 22, 1998 DNA62880-1513 203097 August 4, 1998 1998 DNA67962-1649 203291 September 29, 1998 DNA69555-2867 PTA-1632 April 4, 2000 DNA71162-2764 PTA-860 October 19, 1999 DNA71290-1630 203275 September 22, 1998 DNA76401-1683 203360 October 20, 1998 DNA76541-1675 203409 October 27, 1998 22, 1998 DNA77623-2524 203546 December 22, 1998 15, 1998 1999 DNA84210-2576 203818 March 2, 1999 DNA86576-2595 203868 March 23, 1999 DNA87976-2593 203888 March 30, 1999 DNA92256-2596 203891 March 30, 1999 25, 1999 3, 1999 4, 1999 4, 1999 1999 2000 3, 1999 22, 1999 DNA96872-2674 PTA-550 August 17, 1999 4, 1999 27, 1999 1999 1999 20, 1999 25, 1999 3, 1999 DNA107786-2723 PTA-474 August 3, 1999 DNA108682-2712 PTA-486 August 3, 1999 Table 7 No. Deposit Date DNA108684-2761 PTA-653 September 14, 1999 17, 1999 10, 1999 10, 1999 14, 1999 DNA108738-2767 PTA-862 October 19, 1999 DNA108743-2722 PTA-508 August 10, 1999 14, 1999 14, 1999 31, 1999 17, 1999 DNA108806-2724 PTA-610 August 31, 1999 10, 1999 9, 1999 16, 1999 31, 1999 16, 1999 21, 2000 16, 1999 14, 2000 2000 9, 1999 25, 2000 14, 2000 DNA131652-2876 PTA-1628 April 4, 2000 11, 2000 DNA132162-2770 PTA-950 November 9, 1999 DNA136110-2763 PTA-652 September 14, 1999 28, 2000 2000 25, 2000 21, 2000 2000 DNA145841-2868 PTA-1678 April 11, 2000 DNA148004-2882 PTA-1779 April 25, 2000 DNA149893-2873 PTA-1672 April 11, 2000 Table 7 Material ATCC Dep. No. Deposit Date DNA149930-2884 PTA-1668 April 11, 2000 DNA150157-2898 PTA-1777 April 25, 2000 DNA150163-2842 PTA-1533 2000 PTA-1729 April 18, 2000 DNA164625-2890 PTA-1535 March 21, 2000 DNA57838-1337 203014 June 23, 1998 August 1998 DNA66675-1587 203282 September 22, 1998 DNA76532-1702 203473 November 17, 1998 DNA105849-2704 PTA-473 August 3, 1999 DNA83500-2506 203391 October 29, 1998 These deposits were made under the provisions of the Budapest Treaty on the International Recognition of the Deposit of Microorganisms for the Purpose of Patent Procedure and the Regulations thereunder (Budapest Treaty). This assures maintenance of a viable culture of the deposit for 30 years from the date of deposit. The deposits will be made available by ATCC under the terms of the Budapest Treaty, and subject to an agreement between Genentech, Inc. and ATCC, which assures permanent and unrestricted availability of the progeny of the culture of the deposit to the public upon issuance of the pertinent U. S. patent or upon laying open to the public of any U. S. or foreign patent application, whichever comes first, and assures availability of the progeny to one determined by the U. S. Commissioner of Patents and to be entitled thereto according to 35 USC § 122 and the Commissioner's rules pursuant thereto (including 37 CFR § 1. 14 with particular reference to 886 OG 638).

The assignee of the present application has agreed that if a culture of the materials on deposit should die or be lost or destroyed when cultivated under suitable conditions, the materials will be promptly

replaced on notification with another of the same. Availability of the deposited material is not to be construed as a license to practice the invention in contravention of the rights granted under the authority of any government in accordance with its patent laws.

EXAMPLE 5 : Use of PRO as a hybridization probe The following method describes use of a nucleotide sequence encoding PRO as a hybridization probe.

DNA comprising the coding sequence of full-length or mature PRO as disclosed herein is employed as a probe to screen for homologous DNAs (such as those encoding naturally-occurring variants of PRO) in human tissue cDNA libraries or human tissue genomic libraries.

Hybridization and washing of filters containing either library DNAs is performed under the following high stringency conditions. Hybridization of radiolabeled PRO-derived probe to the filters is performed in a solution of formamide, 5x SSC, 0. SDS, 0. sodium pyrophosphate, 50 mM sodium phosphate, pH 6. 8, 2x Denhardt's solution, and 10% dextran sulfate at for 20 hours. Washing of the filters is performed in an aqueous solution of 0. Ix SSC and 0. 1 % SDS at 42°C.

DNAs having a desired sequence identity with the DNA encoding full-length native sequence PRO can then be identified using standard techniques known in the art.

EXAMPLE 6 : Expression of PRO in E. coli This example illustrates preparation of an unglycosylated form of PRO by recombinant expression in E. coli.

The DNA sequence encoding PRO is initially amplified using selected PCR primers. The primers should contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector.

A variety of expression vectors may be employed. An example of a suitable vector is pBR322 (derived from E. coli ; see Bolivar et Gene, 2 : 95 (1977)) which contains genes for and tetracycline resistance. The vector is digested with restriction enzyme and dephosphorylated. The PCR amplified sequences are then ligated into the vector. The vector will preferably include sequences which, encode for an antibiotic resistance gene, a trp promoter, a polyhis leader (including the first six STII codons, polyhis sequence, and cleavage site), the PRO coding region, lambda transcriptional terminator, and an gene.

The ligation mixture is then used to transform a selected E. coli strain using the methods described in Sambrook et al., supra. Transformants are identified by their ability to grow on LB plates and antibiotic resistant colonies are then selected. Plasmid DNA can be isolated and confirmed by restriction analysis and DNA sequencing.

Selected clones can be grown overnight in liquid culture medium such as LB broth supplemented with antibiotics. The overnight culture may subsequently be used to inoculate a larger scale culture. The cells are then grown to a desired optical density, during which the expression promoter is turned on.

After culturing the cells for several more hours, the cells can be harvested by centrifugation. The cell pellet obtained by the centrifugation can be solubilized using various agents known in the art, and the solubilized PRO protein can then be purified using a metal chelating column under conditions that allow tight binding of the protein.

PRO may be expressed in E. coli in a poly-His tagged form, using the following procedure. The DNA encoding PRO is initially amplified using selected PCR primers. The primers will contain restriction

enzyme sites which correspond to the restriction enzyme sites on the selected expression vector, and other useful sequences providing for efficient and reliable translation initiation, rapid purification on a metal chelation column, and proteolytic removal with enterokinase. The PCR-amplified, poly-His tagged sequences are then ligated into an expression vector, which is used to transform an E. coli host based on strain 52 (W3110 fuhA (tonA) Ion galE rpoHts (htpRts) clpP Transformants are first grown in LB containing 50 mg/ml carbenicillin at 30°C with shaking until an O. D. 600 of 3-5 is reached. Cultures are then diluted 50-100 fold into CRAP media (prepared by mixing 3. 57 g 0. 71 g sodium 1. 07 g 5. 36 g Difco yeast extract, 5. 36 g Sheffield hycase SF in 500 mL water, as well as 110 mM MPOS, pH 7. 3, 0. 55% (w/v) glucose and 7 mM and grown for approximately 20-30 hours at with shaking. Samples are removed to verify expression by SDS-PAGE analysis, and the bulk culture is centrifuged to pellet the cells. Cell pellets are frozen until purification and refolding.

E. coli paste from 0. 5 to 1 L fermentations (6-10 g pellets) is resuspended in 10 volumes (w/v) in 7 M guanidine, 20 mM Tris, pH 8 buffer. Solid sodium sulfite and sodium tetrathionate is added to make final concentrations of 1M and 0. 02 M, respectively, and the solution is stirred overnight at This step results in a denatured protein with all cysteine residues blocked by sulfitolization. The solution is centrifuged at 40, 000 rpm in a Beckman Ultracentifuge for 30 min. The supernatant is diluted with 3-5 volumes of metal chelate column buffer (6 M guanidine, 20 mM Tris, pH 7. 4) and filtered through 0. 22 micron filters to clarify. The clarified extract is loaded onto a 5 Qiagen metal chelate column equilibrated in the metal chelate column buffer. The column is washed with additional buffer containing 50 mM imidazole (Calbiochem, Utrol grade), pH 7. 4. The protein is eluted with buffer containing 250 mM imidazole. Fractions containing the desired protein are pooled and stored at Protein concentration is estimated by its absorbance at 280 nm using the calculated extinction coefficient based on its amino acid sequence.

The proteins are refolded by diluting the sample slowly into freshly prepared refolding buffer consisting of : 20 mM Tris, pH 8. 6, 0. 3 M NaCI, 2. 5 M urea, 5 mM cysteine, 20 mM glycine and 1 mM EDTA. Refolding volumes are chosen so that the final protein concentration is between 50 to 100 The refolding solution is stirred gently at for 12-36 hours. The refolding reaction is quenched by the addition of TFA to a final concentration of 0. 4% (pH of approximately 3). Before further purification of the protein, the solution is filtered through a 0. 22 micron filter and acetonitrile is added to 2-10% final concentration. The refolded protein is chromatographed on a Poros RI/H reversed phase column using a mobile buffer of 0. 1 % TFA with elution with a gradient of acetonitrile from 10 to Aliquots of fractions with A280 absorbance are analyzed on SDS polyacrylamide gels and fractions containing homogeneous refolded protein are pooled. Generally, the properly refolded species of most proteins are eluted at the lowest concentrations of acetonitrile since those species are the most compact with their hydrophobic interiors shielded from interaction with the reversed phase resin.

Aggregated species are usually eluted at higher acetonitrile concentrations. In addition to resolving misfolded forms of proteins from the desired form, the reversed phase step also removes endotoxin from the samples.

Fractions containing the desired folded PRO polypeptide are pooled and the acetonitrile removed using a gentle stream of nitrogen directed at the solution. Proteins are formulated into 20 mM Hepes, pH 6. 8 with 0. 14 M sodium chloride and 4% mannitol by dialysis or by gel filtration using G25 Superfine (Pharmacia) resins equilibrated in the formulation buffer and sterile filtered.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 7 : Expression of PRO in mammalian cells This example illustrates preparation of a potentially glycosylated form of PRO by recombinant expression in mammalian cells.

The vector, (see EP 307, 247, published March 15, 1989), is employed as the expression vector.

Optionally, the PRO DNA is ligated into with selected restriction enzymes to allow insertion of the PRO DNA using ligation methods such as described in Sambrook et al., supra. The resulting vector is called PRO.

In one embodiment, the selected host cells may be 293 cells. Human 293 cells (ATCC CCL 1573) are grown to confluence in tissue culture plates in medium such as DMEM supplemented with fetal calf serum and optionally, nutrient components and/or antibiotics. About DNA is mixed with about DNA encoding the VA RNA gene [Thimmappaya et al., Cell, 31 : 543 (1982)] and dissolved in 500 of 1 mM Tris- 0. 1 mM EDTA, 0. 227 M To this mixture is added, dropwise, of 50 mM HEPES 7. 35), 280 mM NaCl, 1. 5 mM NaPO4, and a precipitate is allowed to form for 10 minutes at The precipitate is suspended and added to the 293 cells and allowed to settle for about four hours at The culture medium is aspirated off and 2 ml of 20 % glycerol in PBS is added for 30 seconds. The 293 cells are then washed with serum free medium, fresh medium is added and the cells are incubated for about 5 days.

Approximately 24 hours after the transfections, the culture medium is removed and replaced with culture medium (alone) or culture medium containing and After a 12 hour incubation, the conditioned medium is collected, concentrated on a spin filter, and loaded onto a SDS gel. The processed gel may be dried and exposed to film for a selected period of time to reveal the presence of PRO polypeptide. The cultures containing transfected cells may undergo further incubation (in serum free medium) and the medium is tested in selected bioassays.

In an alternative technique, PRO may be introduced into 293 cells transiently using the dextran sulfate method described by et al., Proc. Natl. Acad. 12 : 7575 (1981). 293 cells are grown to maximal density in a spinner flask and DNA is added. The cells are first concentrated from the spinner flask by centrifugation and washed with PBS. The DNA-dextran precipitate is incubated on the cell pellet for four hours. The cells are treated with 20% glycerol for 90 seconds, washed with tissue culture medium, and re- introduced into the spinner flask containing tissue culture medium, bovine insulin and 0. bovine transferrin. After about four days, the conditioned media is centrifuged and filtered to remove cells and debris.

The sample containing expressed PRO can then be concentrated and purified by any selected method, such as dialysis and/or column chromatography.

In another embodiment, PRO can be expressed in CHO cells. The can be transfected into CHO cells using known reagents such as CaPO4 or DEAE-dextran. As described above, the cell cultures can be incubated, and the medium replaced with culture medium (alone) or medium containing a radiolabel such as 35S- methionine. After determining the presence of PRO polypeptide, the culture medium may be replaced with serum free medium. Preferably, the cultures are incubated for about 6 days, and then the conditioned medium is harvested. The medium containing the expressed PRO can then be concentrated and purified by any selected method.

Epitope-tagged PRO may also be expressed in host CHO cells. The PRO may be subcloned out of the vector. The insert can undergo PCR to fuse in frame with a selected epitope tag such as a poly-his tag into a Baculovirus expression vector. The poly-his tagged PRO insert can then be subcloned into a SV40 driven vector containing a selection marker such as DHFR for selection of stable clones. Finally, the CHO cells can be transfected (as described above) with the SV40 driven vector. Labeling may be performed, as described above, to verify expression. The culture medium containing the expressed poly-His tagged PRO can then be concentrated and purified by any selected method, such as by affinity

chromatography.

PRO may also be expressed in CHO and/or COS cells by a transient expression procedure or in CHO cells by another stable expression procedure.

Stable expression in CHO cells is performed using the following procedure. The proteins are expressed as an IgG construct (immunoadhesin), in which the coding sequences for the soluble forms (e. g. extracellular domains) of the respective proteins are fused to an constant region sequence containing the hinge, CH2 and CH2 domains and/or is a poly-His tagged form.

Following PCR amplification, the respective DNAs are subcloned in a CHO expression vector using standard techniques as described in Ausubel et al., Current Protocols of Molecular Unit 3. 16, John Wiley and Sons (1997). CHO expression vectors are constructed to have compatible restriction sites 5'and 3'of the DNA of interest to allow the convenient shuttling of cDNA's. The vector used expression in CHO cells is as described in Lucas et al., Nucl. Acids Res. 24 : 9 (1774-1779 (1996), and uses the SV40 early promoter/enhancer to drive expression of the cDNA of interest and dihydrofolate reductase (DHFR). DHFR expression permits selection for stable maintenance of the plasmid following transfection.

Twelve micrograms of the desired plasmid DNA is introduced into approximately 10 million CHO cells using commercially available transfection reagents Superfect (Qiagen), (Boehringer The cells are grown as described in Lucas et al., supra. Approximately 3 x 107 cells are frozen in an ampule for further growth and production as described below.

The ampules containing the plasmid DNA are thawed by placement into water bath and mixed by vortexing. The contents are pipetted into a centrifuge tube containing 10 mLs of media and centrifuged at 1000 rpm for 5 minutes. The supernatant is aspirated and the cells are resuspended in 10 of selective media (0. 2 filtered PS20 with 0. fetal bovine serum). The cells are then aliquoted into a 100 mL spinner containing 90 mL of selective media. After 1-2 days, the cells are transferred into a 250 mL spinner filled with 150 mL selective growth medium and incubated at After another 2-3 days, 250 mL, 500 mL and 2000 mL spinners are seeded with 3 x The cell media is exchanged with fresh media by centrifugation and resuspension in production medium. Although any suitable CHO media may be employed, a production medium described in U. S. Patent No. 5, 122, 469, issued June 16, 1992 may actually be used. A 3L production spinner is seeded at 1. 2 x 106 On day 0, the cell number pH ie determined. On day 1, the spinner is sampled and sparging with filtered air is commenced. On day 2, the spinner is sampled, the temperature shifted to and 30 mL of 500 g/L glucose and 0. 6 mL of 10% antifoam (e. g., 35% emulsion, Dow Coming 365 Medical Grade Emulsion) taken. Throughout the production, the pH is adjusted as necessary to keep it at around 7. 2. After 10 days, or until the viability dropped below the cell culture is harvested by centrifugation and filtering through a 0. um filter. The filtrate was either stored at or immediately loaded onto columns for purification.

For the poly-His tagged constructs, the proteins are purified using a column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml column equilibrated in 20 mM Hepes, pH 7. 4, buffer containing 0. 3 M NaCl and 5 mM imidazole at a flow rate of 4-5 at After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0. 25 M imidazole. The highly purified protein is subsequently desalted into a storage buffer containing 10 mM Hepes, 14 M and 4% mannitol, pH 6. 8, with a 25 G25 Superfine (Pharmacia) column and stored at-80°C.

(Fc-containing) constructs are purified from the conditioned media as follows. The conditioned medium

is pumped onto a 5 ml Protein A column (Pharmacia) which had been equilibrated in 20 mM Na phosphate buffer, pH 6. 8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3. 5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 8 : Expression of PRO in Yeast The following method describes recombinant expression of PRO in yeast.

First, yeast expression vectors are constructed for intracellular production or secretion of PRO from the ADH2/GAPDH promoter. DNA encoding PRO and the promoter is inserted into suitable restriction enzyme sites in the selected plasmid to direct intracellular expression of PRO. For secretion, DNA encoding PRO can be cloned into the selected plasmid, together with DNA encoding the ADH2/GAPDH promoter, a native PRO signal peptide or other mammalian signal peptide, or, for example, a yeast alpha-factor or invertase secretory signal/leader sequence, and linker sequences (if needed) for expression of PRO.

Yeast cells, such as yeast strain can then be transformed with the expression plasmids described above and cultured in selected fermentation media. The transformed yeast can be analyzed by precipitation with 10% trichloroacetic acid and separation by SDS-PAGE, followed by staining of the gels with Coomassie Blue stain.

Recombinant PRO can subsequently be isolated and purified by removing the yeast cells from the fermentation medium by centrifugation and then concentrating the medium using selected cartridge filters. The concentrate containing PRO may further be purified using selected column chromatography resins.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 9 : Expression of PRO in Insect Cells The following method describes recombinant expression of PRO in Baculovirus-infected insect cells.

The sequence coding for PRO is fused upstream of an epitope tag contained within a baculovirus expression vector. Such epitope tags include poly-his tags and immunoglobulin tags (like Fc regions of IgG).

A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pVL1393 (Novagen). Briefly, the sequence encoding PRO or the desired portion of the coding sequence of PRO such as the sequence encoding the extracellular domain of a transmembrane protein or the sequence encoding the mature protein if the protein is extracellular is amplified by PCR with primers complementary to the 5'and 3'regions. The 5'primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector.

Recombinant baculovirus is generated by co-transfecting the above plasmid and virus DNA (Pharmingen) into Spodoptera cells (ATCC CRL 1711) using lipofectin (commercially available from

GIBCO-BRL). After 4-5 days of incubation at the released viruses are harvested and used for further amplifications. Viral infection and protein expression are performed as described by O'Reilley et al., Baculovirus expression vectors : A Laboratory Manual, Oxford : Oxford University Press (1994).

Expressed poly-his tagged PRO can then be purified, for example, by affinity chromatography as follows. Extracts are prepared from recombinant virus-infected Sf9 cells as described by Rupert et Nature, 362 : 175-179 (1993). Briefly, Sf9 cells are washed, resuspended in sonication buffer (25 mL Hepes, pH 9 ; 12. 5 mM ; 0. 1 mM EDTA ; glycerol ; 0. NP-40 ; 0. 4 M and sonicated twice for 20 seconds on ice. The sonicates are cleared by centrifugation, and the supernatant is diluted 50-fold in loading buffer (50 mM phosphate, 300 mM NaCl, glycerol, pH 7. 8) and filtered through a 0. filter.

A agarose column (commercially available from Qiagen) is prepared with a bed volume of 5 washed with 25 of water and equilibrated with 25 mL of loading buffer. The filtered cell extract is loaded onto the column at 0. 5 mL per minute. The column is washed to baseline with loading buffer, at which point fraction collection is started. Next, the column is washed with a secondary wash buffer (50 mM phosphate ; 300 mM NaCl, 10% glycerol, pH 6. 0), which elutes nonspecifically bound protein. After reaching baseline again, the column is developed with a 0 to 500 mM Imidazole gradient in the secondary wash buffer. One mL fractions are collected and analyzed by SDS-PAGE and silver staining or Western blot with to alkaline phosphatase (Qiagen). Fractions containing the eluted PRO are pooled and dialyzed against loading buffer.

Alternatively, purification of the IgG tagged (or Fc tagged) PRO can be performed using known chromatography techniques, including for instance, Protein A or protein G column chromatography.

Many of the PRO polypeptides disclosed herein were successfully expressed as described above.

EXAMPLE 10 : Preparation of Antibodies that Bind PRO This example illustrates preparation of monoclonal antibodies which can specifically bind PRO.

Techniques for producing the monoclonal antibodies are known in the art and are described, for instance, in Goding, supra. Immunogens that may be employed include purified PRO, fusion proteins containing PRO, and cells expressing recombinant PRO on the cell surface. Selection of the can be made by the skilled artisan without undue experimentation.

Mice, such as Balb/c, are immunized with the PRO emulsified in complete Freund's adjuvant and injected subcutaneously or intraperitoneally in an amount from 1-100 micrograms. Alternatively, the immunogen is emulsified in MPL-TDM adjuvant (Ribi Research, Hamilton, MT) and injected into the animal's hind foot pads. The immunized mice are then boosted 10 to 12 days later with additional emulsified in the selected adjuvant. Thereafter, for several weeks, the mice may also be boosted with additional immunization injections. Serum samples may be periodically obtained from the mice by retro-orbital bleeding for testing in ELISA assays to detect anti-PRO antibodies.

After a suitable antibody titer has been detected, the animals"positive"for antibodies can be injected with a final intravenous injection of PRO. Three to four days later, the mice are sacrificed and the spleen cells are harvested. The spleen cells are then fused (using 35 % polyethylene glycol) to a selected murine myeloma cell line such as P3X63AgU. available from ATCC, No. CRL 1597. The fusions generate hybridoma cells which can then be plated in 96 well tissue culture plates containing HAT (hypoxanthine, aminopterin, and thymidine) medium to inhibit proliferation of non-fused cells, myeloma hybrids, and spleen cell hybrids.

The hybridoma cells will be screened in an ELISA for reactivity against PRO. Determination of "positive"hybridoma cells secreting the desired monoclonal antibodies against PRO is within the skill in the art.

The positive hybridoma cells can be injected intraperitoneally into syngeneic Balb/c mice to produce ascites containing the anti-PRO monoclonal antibodies. Alternatively, the hybridoma cells can be grown in tissue culture flasks or roller bottles. Purification of the monoclonal antibodies produced in the ascites can be accomplished using ammonium sulfate precipitation, followed by gel exclusion chromatography. Alternatively, affinity chromatography based upon binding of antibody to protein A or protein G can be employed.

EXAMPLE 11 : Purification of PRO Polypeptides Using Specific Antibodies Native or recombinant PRO polypeptides may be purified by a variety of standard techniques in the art of protein purification. For example, pro-PRO polypeptide, mature PRO polypeptide, or pre-PRO polypeptide is purified by chromatography using antibodies specific for the PRO polypeptide of interest. In general, an column is constructed by covalently coupling the anti-PRO polypeptide antibody to an activated chromatographic resin.

Polyclonal immunoglobulins are prepared from immune sera either by precipitation with ammonium sulfate or by purification on immobilized Protein A (Pharmacia LKB Biotechnology, Piscataway, N. J.). Likewise, monoclonal antibodies are prepared from mouse ascites fluid by ammonium sulfate precipitation or chromatography on immobilized Protein A. Partially purified immunoglobulin is covalently attached to a chromatographic resin such as CnBr-activated SEPHAROSE (Pharmacia LKB Biotechnology). The antibody is coupled to the resin, the resin is blocked, and the derivative resin is washed according to the manufacturer's instructions.

Such an immunoaffinity column is utilized in the purification of PRO polypeptide by preparing a fraction from cells containing PRO polypeptide in a soluble form. This preparation is derived by solubilization of the whole cell or of a fraction obtained via differential centrifugation by the addition of detergent or by other methods well known in the art. Alternatively, soluble PRO polypeptide containing a signal sequence may be secreted in useful quantity into the medium in which the cells are grown.

A soluble PRO polypeptide-containing preparation is passed over the column, and the column is washed under conditions that allow the preferential absorbance of PRO polypeptide (e. g., high ionic strength buffers in the presence of detergent). Then, the column is eluted under conditions that disrupt antibody/PRO polypeptide binding (e. g., a low pH buffer such as approximately pH 2-3, or a high concentration of a chaotrope such as urea or thiocyanate ion), and PRO polypeptide is collected.

EXAMPLE 12 : Drug Screening This invention is particularly useful for screening compounds by using PRO polypeptides or binding fragment thereof in any of a variety of drug screening techniques. The PRO polypeptide or fragment employed in such a test may either be free in solution, affixed to a solid support, borne on a cell surface, or located One method of drug screening utilizes eukaryotic or prokaryotic host cells which are stably transformed with recombinant nucleic acids expressing the PRO polypeptide or fragment. Drugs are screened against such transformed cells in competitive binding assays. Such cells, either in viable or fixed form, can be used for standard binding assays. One may measure, for example, the formation of complexes between PRO polypeptide or a fragment and the agent being tested. Alternatively, one can examine the diminution in complex formation between the PRO polypeptide and its target cell or target receptors caused by the agent being tested.

Thus, the present invention provides methods of screening for drugs or any other agents which can

affect a PRO polypeptide-associated disease or disorder. These methods comprise contacting such an agent with an PRO polypeptide or fragment thereof and assaying (I) for the presence of a complex between the agent and the PRO polypeptide or fragment, or (ii) for the presence of a complex between the PRO polypeptide or fragment and the cell, by methods well known in the art. In such competitive binding assays, the PRO polypeptide or fragment is typically labeled. After suitable incubation, free PRO polypeptide or fragment is separated from that present in bound form, and the amount of free or uncomplexed label is a measure of the ability of the particular agent to bind to PRO polypeptide or to interfere with the PRO complex.

Another technique for drug screening provides high throughput screening for compounds having suitable binding affinity to a polypeptide and is described in detail in WO 84/03564, published on September 13,

Briefly stated, large numbers of different small peptide test compounds are synthesized on a solid substrate, such as plastic pins or some other surface. As applied to a PRO polypeptide, the peptide test compounds are reacted with PRO polypeptide and washed. Bound PRO polypeptide is detected by methods well known in the art.

Purified PRO polypeptide can also be coated directly onto plates for use in the aforementioned drug screening techniques. In addition, non-neutralizing antibodies can be used to capture the peptide and immobilize it on the solid support.

This invention also contemplates the use of competitive drug screening assays in which neutralizing antibodies capable of binding PRO polypeptide specifically compete with a test compound for binding to PRO polypeptide or fragments thereof. In this manner, the antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with PRO polypeptide.

EXAMPLE 13 : Rational Drug Design The goal of rational drug design is to produce structural analogs of biologically active polypeptide of interest (i. e., a PRO polypeptide) or of small molecules with which they interact, e. g., agonists, antagonists, or inhibitors. Any of these examples can be used to fashion drugs which are more active or stable forms of the PRO polypeptide or which enhance or interfere with the function of the PRO polypeptide in vivo Hodgson, : 19-21 (1991)).

In one approach, the three-dimensional structure of the PRO polypeptide, or of an PRO polypeptide-inhibitor complex, is determined by x-ray crystallography, by computer modeling or, most typically, by a combination of the two approaches. Both the shape and charges of the PRO polypeptide must be ascertained to elucidate the structure and to determine active site (s) of the molecule. Less often, useful information regarding the structure of the PRO polypeptide may be gained by modeling based on the structure of homologous proteins.

In both cases, relevant structural information is used to design analogous PRO polypeptide-like molecules or to identify efficient inhibitors. Useful examples of rational drug design may include molecules which have improved activity or stability as shown by Braxton andWells, Biochemistrv. 31 : 7796-7801 (1992) or which act as inhibitors, agonists, or antagonists of native peptides as shown by Athauda et J. Biochem., 113 : 742-746 (1993).

It is also possible to isolate a target-specific antibody, selected by functional assay, as described above, and then to solve its crystal structure. This approach, in principle, yields a upon which subsequent drug design can be based. It is possible to bypass protein crystallography altogether by generating anti-idiotypic antibodies (anti-ids) to a functional, pharmacologically active antibody. As a mirror image of a

mirror image, the binding site of the anti-ids would be expected to be an analog of the original receptor. The anti-id could then be used to identify and isolate peptides from banks of chemically or biologically produced peptides. The isolated peptides would then act as the pharmacore.

By virtue of the present invention, sufficient amounts of the PRO polypeptide may be made available to perform such analytical studies as X-ray crystallography. In addition, knowledge of the PRO polypeptide amino acid sequence provided herein will provide guidance to those employing computer modeling techniques in place of or in addition to x-ray crystallography.

EXAMPLE 14 : Identification of PRO Polypeptides That Stimulate Release In Human Blood (Assay 128) This assay shows that certain PRO polypeptides of the present invention act to stimulate the release of in human blood. PRO polypeptides testing positive in this assay are useful for, among other things, research purposes where stimulation of the release of would be desired and for the therapeutic treatment of conditions wherein enhanced release would be beneficial. Specifically, 200 of human blood supplemented with 50mM Hepes buffer (pH 7. 2) is aliquoted per well in a 96 well test plate. To each well is then added of either the test PRO polypeptide in 50 mM Hepes buffer (at various concentrations) or 50 mM Hepes buffer alone (negative control) and the plates are incubated at for 6 hours. The samples are then centrifuged and of plasma is collected from each well and tested for the presence of by ELISA assay. A positive in the assay is a higher amount of in the PRO polypeptide treated samples as compared to the negative control samples.

The following PRO polypeptides tested positive in this assay : PRO1343,

EXAMPLE 15 : Promotion of Chondrocyte Redifferentiation (Assay 129) This assay is designed to determine whether PRO polypeptides of the present invention show the ability to induce the proliferation and/or redifferentiation of chondrocytes in culture. PRO polypeptides testing positive in this assay would be expected to be useful for the therapeutic treatment of various bone and/or cartilage disorders such as, for example, sports injuries and arthritis.

Porcine chondrocytes are isolated by overnight collagenase digestion of articular cartilage of the metacarpophalangeal joint of 4-6 month old female pigs. The isolated cells are then seeded at 25, 000 in Ham F-12 containing 10% FBS and 4 gentamycin. The culture media is changed every third day. On day 12, the cells are seeded in 96 well plates at 5, 000 cells/well in of the same media without serum and of either serum-free medium (negative control), staurosporin (final concentration of 5 nM ; positive control) or the test PRO polypeptide are added to give a final volume of After 5 days at of media comtaining Hoechst 33342 and 50 5-CFDA is added to each well and incubated for an additional 10 minutes at A picture of the green fluorescence is taken for each well and the differentiation state of the chondrocytes is calculated by morphometric analysis. A positive result in the assay is obtained when the > 50 % of the PRO polypeptide treated cells are differentiated (compared to the background obtained by the negative control).

PR06029 polypeptide tested positive in this assay.

EXAMPLE 16 : to Detect of PRO Polypeptides in Cancerous Tumors Nucleic acid microarrays, often containing thousands of gene sequences, are useful for identifying differentially expressed genes in diseased tissues as compared to their normal counterparts. Using nucleic acid microarrays, test and control samples from test and control tissue samples are reverse transcribed and labeled to generate cDNA probes. The cDNA probes are then hybridized to an array of nucleic acids immobilized on a solid support. The array is configured such that the sequence and position of each member of the array is known. For example, a selection of genes known to be expressed in certain disease states may be

arrayed on a solid support. Hybridization of a labeled probe with a particular array member indicates that the sample from which the probe was derived expresses that gene. If the hybridization signal of a probe from a test (disease tissue) sample is greater than hybridization signal of a probe from a control (normal tissue) sample, the gene or genes overexpressed in the disease tissue are identified. The implication of this result is that an overexpressed protein in a diseased tissue is useful not only as a diagnostic marker for the presence of the disease condition, but also as a therapeutic target for treatment of the disease condition.

The methodology of hybridization of nucleic acids and microarray technology is well known in the art.

In the present example, the specific preparation of nucleic acids for hybridization and probes, slides, and hybridization conditions are all detailed in U. S. Provisional Patent Application Serial No. 60/193, 767, filed on March 31, 2000 and which is herein incorporated by reference.

In the present example, cancerous tumors derived from various human tissues were studied for PRO polypeptide-encoding gene expression relative to non-cancerous human tissue in an attempt to identify those PRO polypeptides which are overexpressed in cancerous tumors. Two sets of experimental data were generated. In one set, cancerous human colon tumor tissue and matched non-cancerous human colon tumor tissue from the same patient ("matched colon control") were obtained and analyzed for PRO polypeptide expression using the above described microarray technology. In the second set of data, cancerous human tumor tissue from any of a variety of different human tumors was obtained and compared to a"universal"epithelial control sample which was prepared by pooling non-cancerous human tissues of epithelial origin, including liver, kidney, and lung. isolated from the pooled tissues represents a mixture of expressed gene products from these different tissues.

Microarray hybridization experiments using the pooled control samples generated a linear plot in a 2-color analysis. The slope of the line generated in a 2-color analysis was then used to normalize the ratios of (test : control detection) within each experiment. The normalized ratios from various experiments were then compared and used to identify clustering of gene expression. Thus, the pooled"universal control"sample not only allowed effective relative gene expression determinations in a simple 2-sample comparison, it also allowed multi-sample comparisons across several experiments.

In the present experiments, nucleic acid probes derived from the herein described PRO polypeptide-encoding nucleic acid sequences were used in the creation of the microarray and RNA from the tumor tissues listed above were used for the hybridization thereto. A value based upon the normalized ratio : experimental ratio was designated as a"cutoff ratio". Only values that were above this cutoff ratio were determined to be significant. Table 8 below shows the results of these experiments, demonstrating that various PRO polypeptides of the preent invention are significantly overexpressed in various human tumor tissues as compared to a non- cancerous human tissue control. As described above, these data demonstrate that the PRO polypeptides of the present invention are useful not only as diagnostic markers for the presence of one or more cancerous tumors, but also serve as therapeutic targets for the treatment of those tumors.

Table 8 Molecule is overexpressed in : as compared to : lung tumor universal normal control PR0284 colon tumor universal normal control PR0284 lung tumor universal normal control PR0284 breast tumor universal normal control tumor universal normal control lung tumor universal normal control breast tumor universal normal control prostate tumor universal normal control colon tumor universal normal control lung tumor universal normal control breast tumor universal normal control colon tumor universal normal control lung tumor universal normal control breast tumor universal normal control colon tumor universal normal control lung tumor universal normal control breast tumor universal normal control cervical tumor universal normal control PR0218 colon tumor universal normal control PR0218 lung

tumor universal normal control PR0260 colon tumor universal normal control PR0260 lung tumor universal normal control PR0260 breast tumor universal normal control PR0260 rectal tumor universal normal control PR0233 colon tumor universal normal control PR0233 lung tumor universal normal control PR0233 breast tumor universal normal control Table 8 in : as compared to : PRO234 colon tumor universal normal control PRO234 lung tumor universal normal control PRO234 breast tumor universal normal control PRO234 liver tumor universal normal control PRO236 colon tumor universal normal control PRO236 lung tumor universal normal control PRO236 breast tumor universal normal control control PRO244 lung tumor universal normal control PRO262 colon tumor universal normal control PRO262 lung tumor universal normal control PRO262 breast tumor universal normal control PRO271 colon tumor universal normal control PRO271 lung tumor universal normal control PRO268 colon tumor universal normal control PRO268 lung tumor universal normal control PRO268 breast tumor universal normal control PR0270 colon tumor universal normal control PRO270 lung tumor universal normal control PR0270 breast tumor universal normal control PRO270 liver tumor universal normal control normal control normal control normal control PRO298 colon tumor universal normal control PRO298 lung tumor universal normal control normal control normal control PRO299 lung tumor universal normal control PRO299 breast tumor universal normal control PR0296 colon tumor universal normal control PRO296 breast tumor universal normal control PR0329 colon tumor universal normal control PRO329 lung tumor universal normal control PRO329 breast tumor universal normal control PR0330 colon tumor universal normal control PRO330 lung tumor universal normal control PRO294 lung tumor universal normal control normal control PRO300 colon tumor universal normal control PRO300 lung tumor universal normal control PR0300 breast tumor universal normal control PRO307 lung tumor universal normal control normal control normal control normal control normal control normal control PRO352 colon tumor universal normal control PRO352 lung tumor universal normal control PRO352 breast tumor universal normal control PRO352 liver tumor universal normal control PRO710 breast tumor universal normal control normal control normal control Table 8 Moleculeis overexpressed in : as compared to : normal control normal control normal control normal control normal control normal control PRO1151 breast tumor universal normal control PRO382 colon tumor universal normal control PR0382 lung tumor universal normal control PRO382 breast tumor universal normal control PRO1864 lung tumor universal normal control PRO breast tumor universal normal control PRO1864 liver tumor universal normal control PRO386 colon tumor universal normal control PRO386 lung tumor universal normal control PRO386 prostate tumor universal normal control normal control normal control normal control PRO852 breast tumor universal normal control PR0700 colon tumor universal normal control PRO700 lung tumor universal normal control PRO700 breast tumor universal normal control PRO700 rectal tumor universal normal control -PRO708 colon tumor universal normal control PRO708 lung tumor universal normal control PR0708 breast tumor universal normal control PR0707 colon tumor universal normal control PRO707 lung tumor universal normal control PRO864 colon tumor universal normal control PRO864 lung tumor universal normal control PRO864 breast tumor universal normal control PR0706 colon tumor universal normal control PRO706 lung tumor universal normal control PRO706 breast tumor universal normal control PRO706 liver tumor universal normal control PRO732 lung tumor universal normal control PRO732 breast tumor universal normal control PRO732 cervical tumor universal normal control normal control normal control normal control normal control normal control normal control normal control PRO872 lung tumor universal normal control PRO872 breast tumor universal normal control PRO872 liver tumor universal normal control PR0704 colon tumor universal normal control PRO704 lung tumor universal normal control PR0704 breast tumor universal normal control PRO705 lung tumor universal normal control PRO705 breast tumor universal normal control Table 8 in : as compared to : normal control normal control normal control PRO702 lung tumor universal normal control normal control normal control normal control normal control normal control normal control normal control normal control normal control normal control PRO1082 lung tumor universal normal control PRO1082 breast tumor universal normal control PRO colon tumor universal normal control PRO lung tumor universal normal control normal control normal control normal control normal control normal control normal control normal control normal control normal control normal control normal control normal control normal

control normal control PRO940 colon tumor universal normal control PRO940 lung tumor universal normal control PRO940 breast tumor universal normal control PRO768 colon tumor universal normal control PRO768 lung tumor universal normal control PRO768 breast tumor universal normal control PRO1079 colon tumor universal normal control PRO lung tumor universal normal control PRO1079 breast tumor universal normal control PRO1079 rectal tumor universal normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO1018 colon tumor universal normal control PRO1018 lung tumor universal normal control PRO1018 breast tumor universal normal control normal control normal control normal control normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO1773 prostate tumor universal normal control PRO1014 lung tumor universal normal control PRO1014 breast tumor universal normal control PRO1013 colon tumor universal normal control Table 8 in : as compared to : PRO lung tumor universal normal control PRO breast tumor universal normal control PRO1013 liver tumor universal normal control control normal control normal control control normal control PRO lung tumor universal normal control PRO breast tumor universal normal control PRO rectal tumor universal normal control PR0842 colon tumor universal normal control PR0842 lung tumor universal normal control PRO842 breast tumor universal normal control normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO1180 liver tumor universal normal control PRO1134 lung tumor universal normal control PRO1134 breast tumor universal normal control PRO1134 prostate tumor universal normal control PRO1115 colon tumor universal normal control PRO1115 lung tumor universal normal control PRO1115 breast tumor universal normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO lung tumor universal normal control PRO breast tumor universal normal control PRO cervical tumor universal normal control normal control PRO827 lung tumor universal normal control PRO827 prostate tumor universal normal control PRO827 cervical tumor universal normal control PRO1057 lung tumor universal normal control PRO1057 breast tumor universal normal control PRO1113 colon tumor universal normal control PRO1113 lung tumor universal normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO breast tumor universal normal control PRO rectal tumor universal normal control PRO lung tumor universal normal control PRO rectal tumor universal normal control PRO1073 lung tumor universal normal control PRO breast tumor universal normal control PRO1136 colon tumor universal normal control PRO1136 lung tumor universal normal control PRO1136 breast tumor universal normal control PRO lung tumor universal normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO breast tumor universal normal control PRO rectal tumor universal normal control PRO1110 colon tumor universal normal control Table 8 in : as compared to : PRO1110 lung tumor universal normal control PRO breast tumor universal normal control PRO1378 colon tumor universal normal control PRO1378 lung tumor universal normal control PRO1378 prostate tumor universal normal control PRO1378 cervical tumor universal normal control PRO1481 colon tumor universal normal control PRO lung tumor universal normal control PRO1109 lung tumor universal normal control PRO breast tumor universal normal control PRO1383 colon tumor universal normal control PRO1383 lung tumor universal normal control PRO1383 breast tumor universal normal control PRO lung tumor universal normal control PRO1189 colon tumor universal normal control PRO lung tumor universal normal control PRO1189 breast tumor universal normal control PRO1189 prostate tumor universal normal control PRO1003 colon tumor universal normal control PRO1003 lung tumor universal normal control PRO1003 breast tumor universal normal control PRO1003 liver tumor universal normal control PRO1003 rectal tumor universal normal control PRO1108 colon tumor universal normal control PRO1108 lung tumor universal normal control PRO1108 breast tumor universal normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO breast tumor universal normal control PRO1138 colon tumor universal normal control PRO lung tumor universal normal control PRO1138 breast tumor universal normal control PRO colon tumor universal normal control PRO1415 lung tumor universal normal control PRO1415 prostate tumor universal normal control PRO lung tumor universal normal control PRO breast tumor universal normal control normal control normal control normal control PRO1069 lung tumor universal normal control

PRO1069 breast tumor universal normal control PRO colon tumor universal normal control PRO1411 lung tumor universal normal control PRO1129 lung tumor universal normal control PRO1129 rectal tumor universal normal control PRO colon tumor universal normal control PRO1359 lung tumor universal normal control PRO1359 breast tumor universal normal control PRO1359 prostate tumor universal normal control PRO lung tumor universal normal control PRO lung tumor universal normal control PRO1028 colon tumor universal normal control PRO1028 lung tumor universal normal control Table 8 in : as compared to : PRO breast tumor universal normal control PRO1028 cervical tumor universal normal control PRO colon tumor universal normal control PRO1027 lung tumor universal normal control PRO1027 breast tumor universal normal control PRO1140 colon tumor universal normal control PRO1140 breast tumor universal normal control PRO colon tumor universal normal control PRO breast tumor universal normal control PRO1105 colon tumor universal normal control PRO lung tumor universal normal control PRO lung tumor universal normal control PRO prostate tumor universal normal control PRO1104 colon tumor universal normal control PRO1104 lung tumor universal normal control PRO1104 breast tumor universal normal control PRO1100 colon tumor universal normal control PRO1100 lung tumor universal normal control PRO1100 breast tumor universal normal control PRO1100 rectal tumor universal normal control PRO1141 lung tumor universal normal control PRO1772 colon tumor universal normal control PRO lung tumor universal normal control PRO1772 breast tumor universal normal control PRO1772 cervical tumor universal normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO cervical tumor universal normal control normal control normal control PRO3566 colon tumor universal normal control PR03566 lung tumor universal normal control PRO lung tumor universal normal control PRO breast tumor universal normal control PRO prostate tumor universal normal control PRO colon tumor universal normal control PRO1098 lung tumor universal normal control PRO rectal tumor universal normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO breast tumor universal normal control PRO1248 lung tumor universal normal control PRO breast tumor universal normal control PRO1127 colon tumor universal normal control PRO1127 lung tumor universal normal control PRO1127 breast tumor universal normal control PRO1316 colon tumor universal normal control PRO lung tumor universal normal control PRO1316 breast tumor universal normal control PRO colon tumor universal normal control PRO1197 lung tumor universal normal control PRO1197 breast tumor universal normal control Table 8 Moleculeis overexpressed in : as compared to : PRO1125 lung tumor universal normal control PRO1158 breast tumor universal normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO breast tumor universal normal control PRO1380 liver tumor universal normal control PRO colon tumor universal normal control PRO1377 lung tumor universal normal control PRO lung tumor universal normal control PRO breast tumor universal normal control PRO lung tumor universal normal control PRO breast tumor universal normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO breast tumor universal normal control PRO3572 lung tumor universal normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO breast tumor universal normal control PRO lung tumor universal normal control PRO breast tumor universal normal control PRO lung tumor universal normal control PRO breast tumor universal normal control PRO1357 colon tumor universal normal control PRO1357 lung tumor universal normal control PRO1557 colon tumor universal normal control PRO1557 lung tumor universal normal control PRO1557 breast tumor universal normal control PRO1305 colon tumor universal normal control PRO1305 lung tumor universal normal control PRO1305 breast tumor universal normal control PRO colon tumor universal normal control PRO1302 lung tumor universal normal control PRO breast tumor universal normal control PRO1302 rectal tumor universal normal control PRO colon tumor universal normal control PRO1336 colon tumor universal normal control PRO lung tumor universal normal control PRO1336 breast tumor universal normal control PRO1278 colon tumor universal normal control PRO1278 lung tumor universal normal control

PRO1270 breast tumor universal normal control PRO1298 colon tumor universal normal control PRO lung tumor universal normal control PRO1301 lung tumor universal normal control PRO breast tumor universal normal control PRO1268 colon tumor universal normal control PRO breast tumor universal normal control PRO1327 lung tumor universal normal control PRO1327 breast tumor universal normal control Table 8 (cont') in : as compared to : PRO1328 colon tumor universal normal control PRO lung tumor universal normal control PRO1328 breast tumor universal normal control PRO1329 colon tumor universal normal control PRO lung tumor universal normal control PRO1329 breast tumor universal normal control PRO1339 colon tumor universal normal control PRO1339 lung tumor universal normal control PRO1342 colon tumor universal normal control PRO1342 lung tumor universal normal control PRO1342 breast tumor universal normal control PRO1342 rectal tumor universal normal control PRO1487 colon tumor universal normal control PRO1487 breast tumor universal normal control normal control normal control PRO1472 colon tumor universal normal control PRO1472 lung tumor universal normal control PRO1385 lung tumor universal normal control PRO1385 breast tumor universal normal control PRO1461 colon tunior universal normal control PRO1461 lung tumor universal normal control PRO1461 breast tumor universal normal control PRO1429 colon tumor universal normal control PRO1429 lung tumor universal normal control PRO1429 breast tumor universal normal control PRO1568 lung tumor universal normal control PRO1568 breast tumor universal normal control PRO1569 colon tumor universal normal control PRO1569 lung tumor universal normal control . PRO1569 breast tumor universal normal control PRO1753 colon tumor universal normal control PRO1753 lung tumor universal normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO breast tumor universal normal control PRO prostate tumor universal normal control PRO rectal tumor universal normal control PRO1559 colon tumor universal normal control PRO1559 lung tumor universal normal control PRO1559 breast tumor universal normal control PRO lung tumor universal normal control PRO breast tumor universal normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO breast tumor universal normal control PRO rectal tumor universal normal control PRO lung tumor universal normal control PRO breast tumor universal normal control PRO1482 lung tumor universal normal control PRO breast tumor universal normal control PRO1409 colon tumor universal normal control PRO lung tumor universal normal control PRO1409 breast tumor universal normal control Table 8 in : as compared to : PRO colon tumor universal normal control PRO lung tumor universal normal control PRO breast tumor universal normal control PRO prostate tumor universal normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO1604 breast tumor universal normal control PRO1491 colon tumor universal normal control PRO1491 lung tumor universal normal control PRO1491 breast tumor universal normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO breast tumor universal normal control PRO1571 colon tumor universal normal control PRO1571 lung tumor universal normal control PRO1571 breast tumor universal normal control PRO lung tumor universal normal control PRO prostate tumor universal normal control PRO lung tumor universal normal control PRO breast tumor universal normal control PRO lung tumor universal normal control PRO breast tumor universal normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO1564 colon tumor universal normal control PRO lung tumor universal normal control PRO1564 breast tumor universal normal control PRO1550 colon tumor universal normal control PRO1550 lung tumor universal normal control PRO1550 breast tumor universal normal control PRO1757 lung tumor universal normal control PRO breast tumor universal normal control PRO1757 prostate tumor universal normal control PRO lung tumor universal normal control PRO1781 colon tumor universal normal control PRO lung tumor universal normal control PRO1781 breast tumor universal normal control PRO1606 lung tumor universal normal control PRO breast tumor universal normal control PRO1784 colon tumor universal normal control PRO1784 lung tumor universal normal control PRO1784 breast tumor universal normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO breast tumor universal normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO1605

prostate tumor universal normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO cervical tumor universal normal control PRO lung tumor universal normal control Table 8 in : as compared to : PRO1865 liver tumor universal normal control PRO1925 lung tumor universal normal control PRO1926 liver tumor universal normal control PR02630 colon tumor universal normal control PRO2630 lung tumor universal normal control PRO2630 breast tumor universal normal control PRO2630 liver tumor universal normal control normal control normal control normal control PRO3301 colon tumor universal normal control PRO3301 lung tumor universal normal control PR03301 breast tumor universal normal control PRO3301 rectal tumor universal normal control PRO3442 colon tumor universal normal control PRO3442 lung tumor universal normal control PRO3442 rectal tumor universal normal control normal control normal control normal control normal control PRO5801 colon tumor universal normal control PRO5801 breast tumor universal normal control PRO19630 colon tumor universal normal control PRO203 colon tumor universal normal control PRO204 colon tumor universal normal control PRO204 lung tumor universal normal control PRO204 breast tumor universal normal control PRO204 prostate tumor universal normal control PRO210 colon tumor universal normal control PRO210 lung tumor universal normal control PRO223 lung tumor universal normal control PRO223 breast tumor universal normal control PRO247 colon tumor universal normal control PRO247 lung tumor universal normal control PRO247 breast universal normal control normal control normal control normal control PRO724 lung tumor universal normal control PRO868 colon tumor universal normal control PRO868 lung tumor universal normal control PRO868 prostate tumor universal normal control PRO868 rectal tumor universal normal control PRO740 colon tumor universal normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO colon tumor universal normal control PRO162 lung tumor universal normal control PRO breast tumor universal normal control PRO828 colon tumor universal normal control PRO828 lung tumor universal normal control PRO828 breast tumor universal normal control PRO828 cervical tumor universal normal control Table 8 in : as compared to : PRO828 liver tumor universal normal control lung tumor universal normal control breast tumor universal normal control rectal tumor universal normal control colon tumor universal normal control lung tumor universal normal control PRO813 breast tumor universal normal control prostate tumor universal normal control PRO1194 colon tumor universal normal control PRO1194 lung tumor universal normal control PRO1194 breast tumor universal normal control PRO887 colon tumor universal normal control PRO887 lung tumor universal normal control PRO887 rectal tumor universal normal control PRO1071 colon tumor universal normal control PRO1071 lung tumor universal normal control PRO1071 breast tumor universal normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO breast tumor universal normal control PRO1190 lung tumor universal normal control PRO1190 breast tumor universal normal control normal control PRO1155 colon tumor universal normal control PRO1155 lung tumor universal normal control PRO breast tumor universal normal control PRO cervical tumor universal normal control PRO1122 lung tumor universal normal control PRO breast tumor universal normal control PRO1183 colon tumor universal normal control PRO1183 lung tumor universal normal control PRO1183 breast tumor universal normal control PRO1337 colon tumor universal normal control PRO lung tumor universal normal control PRO1337 breast tumor universal normal control PRO1480 colon tumor universal normal control PRO1480 lung tumor universal normal control PRO1480 breast tumor universal normal control PRO19645 colon tumor universal normal control PRO9782 colon tumor universal normal control PRO1419 colon tumor universal normal control PRO colon tumor universal normal control PRO lung tumor universal normal control PRO colon tumor universal normal control PRO1567 lung tumor universal normal control PRO breast tumor universal normal control PRO1891 colon tumor universal normal control PRO1889 colon tumor universal normal control PRO lung tumor universal normal control PRO1785 lung tumor universal normal control PRO1785 prostate tumor universal normal control PRO6003 colon tumor universal normal control normal control PRO4356 colon tumor universal normal control Table 8 Molecule is overexpressed in : as compared to : PRO4352 colon tumor universal normal control normal control normal control normal control PR04369 colon tumor universal normal control PR06030 colon tumor universal normal control normal control PR04424

colon tumor universal normal control PRO4424 breast tumor universal normal control PRO6017 colon tumor universal normal control PRO19563 colon tumor universal normal control PRO6015 colon tumor universal normal control normal control PRO5776 colon tumor universal normal control PRO4430 lung tumor universal normal control PRO4421 colon tumor universal normal control normal control PRO4423 colon tumor universal normal control normal control normal control PRO4501 colon tumor universal normal control PRO6240 colon tumor universal normal control PRO6245 colon tumor universal normal control PRO6175 colon tumor universal normal control PRO9742 colon tumor universal normal control normal control PRO6239 colon tumor universal normal control PRO6493 colon tumor universal normal control normal control PRO9822 colon tumor universal normal control PRO6244 colon tumor universal normal control PRO9740 colon tumor universal normal control normal control normal control normal control PRO6246 colon tumor universal normal control PRO6241 colon tumor universal normal control normal control normal control normal control PRO9856 colon tumor universal normal control PRO19605 colon tumor universal normal control normal control PRO12970 colon tumor universal normal control PRO19626 colon tumor universal normal control PR09883 colon tumor universal normal control PRO19670 colon tumor universal normal control PRO19624 colon tumor universal normal control PRO colon tumor universal normal control PRO19675 colon tumor universal normal control normal control normal control PRO19644 colon tumor universal normal control PRO19625 colon tumor universal normal control Table 8 in : as compared to : PRO19597 colon tumor universal normal control PRO16090 colon tumor universal normal control PRO19576 colon tumor universal normal control PRO19646 colon tumor universal normal control PRO19814 colon tumor universal normal control PRO19669 colon tumor universal normal control PRO19818 colon tumor universal normal control PRO20088 colon tumor universal normal control PRO16089 colon tumor universal normal control PRO20025 colon tumor universal normal control PRO20040 colon tumor universal normal control PRO adrenal tumor universal normal control PRO breast tumor universal normal control PRO cervical tumor universal normal control PRO colon tumor universal normal control PRO1760 liver tumor universal normal control PRO lung tumor universal normal control PRO prostate tumor universal normal control PRO rectal tumor universal normal control PR06029 adrenal tumor universal normal control PRO6029 colon tumor universal normal control PR06029 prostate tumor universal normal control PRO1801 colon tumor universal normal control PRO1801 lung tumor universal normal control

WHAT IS CLAIMED IS : 1. Isolated nucleic acid having at least 80 % nucleic acid sequence identity to a nucleotide sequence that encodes an amino acid sequence selected from the group consisting of the amino acid sequence shown in Figure 2 (SEQ ID NO : 2), Figure 4 (SEQ ID NO : 4), Figure 6 (SEQ ID NO : 6), Figure 8 (SEQ ID NO : Figure 10 (SEQ ID NO : 10), Figure 12 (SEQ ID NO : 12), Figure 14 (SEQ ID N0 : 14), Figure 16 (SEQ ID NO : 16), Figure 18 (SEQ ID NO : 18), Figure 20 (SEQ ID NO : 20), Figure 22 (SEQ ID NO : 22), Figure 24 (SEQ ID NO : 24), Figure 26 (SEQ ID NO : 26), Figure 28 (SEQ ID NO : 28), Figure 30 (SEQ ID NO : 30), Figure 32 (SEQ ID NO : 32), Figure 34 (SEQ ID NO : 34), Figure 36 (SEQ ID NO : 36), Figure 38 (SEQ ID NO : 38), Figure 40 (SEQ ID NO : 40), Figure 42 (SEQ ID NO : 42), Figure 44 (SEQ ID NO : 44), Figure 46 (SEQ ID NO : 46), Figure 48 (SEQ ID NO : Figure 50 (SEQ ID NO : 50), Figure 52 (SEQ ID NO : 52), Figure 54 (SEQ ID NO : 54), Figure 56 (SEQ ID NO : 56), Figure 58 (SEQ ID NO : Figure 60 (SEQ ID NO : 60), Figure 62 (SEQ ID NO : 62), Figure 64 (SEQ ID NO : 64), Figure 66 (SEQ ID NO : 66), Figure 68 (SEQ ID NO : 68), Figure 70 (SEQ ID NO : 70), Figure 72 (SEQ ID NO : 72), Figure 74 (SEQ ID NO : 74), Figure 76 (SEQ ID NO : 76), Figure 78 (SEQ ID NO : 78), Figure 80 (SEQ ID NO : 80), Figure 82 (SEQ ID NO : 82), Figure 84 (SEQ ID NO : 84), Figure 86 (SEQ ID NO : 86), Figure 88 (SEQ ID NO : 88), Figure 90 (SEQ ID NO : 90), Figure 92 (SEQ ID NO : 92), Figure 94 (SEQ ID NO : 94), Figure 96 (SEQ ID NO : 96), Figure 98 (SEQ ID NO : 98), Figure 100 (SEQ ID NO : 100), Figure 102 (SEQ ID NO : 102), Figure 104 (SEQ ID NO : 104), Figure 106 (SEQ ID NO : 106), Figure 108 (SEQ ID NO : Figure 110 (SEQ ID NO : 110), Figure 112 (SEQ ID NO : 112), Figure 114 (SEQ ID NO : 114), Figure 116 (SEQ ID NO : 116), Figure 118 (SEQ ID NO : 118), Figure 120 (SEQ ID NO : 120), Figure 122 (SEQ ID NO : 122), Figure 124

(SEQ ID NO : 124), Figure 126 (SEQ ID NO : 126), Figure 128 (SEQ ID NO : 128), Figure 130 (SEQ ID NO : 130), Figure 132 (SEQ ID NO : 132), Figure 134 (SEQ ID NO : 134), Figure 136 (SEQ ID NO : 136), Figure 138 (SEQ ID NO : 138), Figure 140 (SEQ ID NO : 140), Figure 142 (SEQ NO : 142), Figure 144 (SEQ ID NO : 144), Figure 146 (SEQ ID NO : 146), Figure 148 (SEQ ID NO : 148), Figure 150 (SEQ ID NO : 150), Figure 152 (SEQ ID NO : 152), Figure 154 (SEQ ID NO : 154), Figure 156 (SEQ ID NO : 156), Figure 158 (SEQ ID NO : 158), Figure 160 (SEQ ID NO : 160), Figure 162 (SEQ ID NO : 162), Figure 164 (SEQ ID NO : 164), Figure 166 (SEQ ID NO : 166), Figure 168 (SEQ ID NO : 168), Figure 170 (SEQ ID NO : 170), Figure 172 (SEQ ID NO : 172), Figure 174 (SEQ ID NO : 174), Figure 176 (SEQ ID NO : 176), Figure 178 (SEQ ID NO : 178), Figure 180 (SEQ ID NO : 180), Figure 182 (SEQ ID NO : Figure 184 (SEQ ID NO : 184), Figure 186 (SEQ ID NO : 186), Figure 188 (SEQ ID NO : 188), Figure 190 (SEQ ID NO : Figure 192 (SEQ ID NO : 192), Figure 194 (SEQ ID NO : 194), Figure 196 (SEQ ID NO : 196), Figure 198 (SEQ ID NO : 198), Figure 200 (SEQ ID NO : 200), Figure 202 (SEQ ID NO : 202), Figure 204 (SEQ ID NO : 204), Figure 206 (SEQ ID NO : 206), Figure 208 (SEQ ID NO : 208), Figure 210 (SEQ ID NO : 210), Figure 212 (SEQ ID NO : 212), Figure 214 (SEQ ID NO : 214), Figure 216 (SEQ ID NO : 216), Figure 218 (SEQ ID NO : 218), Figure 220 (SEQ ID NO : 220), Figure 222 (SEQ ID NO : 222), Figure 224 (SEQ ID NO : 224), Figure 226 (SEQ ID NO : 226), Figure 228 (SEQ ID NO : 228), Figure 230 (SEQ ID NO : 230), Figure 232 (SEQ ID NO : 232), Figure 234 (SEQ ID NO : 234), Figure 236 (SEQ ID NO : 236), Figure 238 (SEQ ID NO : 238), Figure 240 (SEQ ID NO : 240), Figure 242 (SEQ ID NO : 242), Figure 244 (SEQ ID NO : 244), Figure 246 (SEQ ID NO : 246), Figure 248 (SEQ ID NO : 248), Figure 250 (SEQ ID NO : 250), Figure 252 (SEQ ID NO : 252), Figure 254 (SEQ ID NO : 254), Figure 256 (SEQ ID NO : 256), Figure 258 (SEQ ID NO : 258), Figure 260 (SEQ ID NO : 260), Figure 262 (SEQ ID NO : 262), Figure 264 (SEQ ID NO : 264), Figure 266 (SEQ ID NO : 266), Figure 268 (SEQ ID NO : 268), Figure 270 (SEQ ID NO : 270), Figure 272 (SEQ ID NO : 272), Figure 274 (SEQ ID NO : 274), Figure 276 (SEQ ID NO : 276), Figure 278 (SEQ ID NO : 278), Figure 280 (SEQ ID NO : Figure 282 (SEQ ID NO : 282), Figure 284 (SEQ ID NO : 284), Figure 286 (SEQ ID NO : 286), Figure 288 (SEQ ID NO : Figure 290 (SEQ ID NO : 290), Figure 292 (SEQ ID NO : 292), Figure 294 (SEQ ID NO : 294), Figure 296 (SEQ ID NO : 296), Figure 298 (SEQ ID NO : 298), Figure 300 (SEQ ID NO : 300), Figure 302 (SEQ ID NO : 302), Figure 304 (SEQ ID NO : 304), Figure 306 (SEQ ID NO : 306), Figure 308 (SEQ ID NO : 308), Figure 310 (SEQ ID NO : 310), Figure 312 (SEQ ID NO : 312), Figure 314 (SEQ ID NO : 314), Figure 316 (SEQ ID NO : 316), Figure 318 (SEQ ID NO : 318), Figure 320 (SEQ ID NO : 320), Figure 322 (SEQ ID NO : 322), Figure 324 (SEQ ID NO : 324), Figure 326 (SEQ ID NO : 326), Figure 328 (SEQ ID NO : 328), Figure 330 (SEQ ID NO : 330), Figure 332 (SEQ ID NO : 332), Figure 334 (SEQ ID NO : 334), Figure 336 (SEQ ID NO : 336), Figure 338 (SEQ ID NO : 338), Figure 340 (SEQ ID NO : 340), Figure 342 (SEQ ID NO : 342), Figure 344 (SEQ ID NO : 344), Figure 346 (SEQ ID NO : 346), Figure 348 (SEQ ID NO : 348), Figure 350 (SEQ ID NO : 350), Figure 352 (SEQ ID NO : 352), Figure 354 (SEQ ID NO : 354), Figure 356 (SEQ ID NO : 356), Figure 358 (SEQ ID NO : 358), Figure 360 (SEQ ID NO : 360), Figure 362 (SEQ ID NO : 362), Figure 364 (SEQ ID NO : 364), Figure 366 (SEQ ID NO : 366), Figure 368 (SEQ ID NO : 368), Figure 370 (SEQ ID NO : 370), Figure 372 (SEQ ID NO : 372), Figure 374 (SEQ ID NO : 374), Figure 376 (SEQ ID NO : 376), Figure 378 (SEQ ID NO : 378), Figure 380 (SEQ ID NO : 380), Figure 382 (SEQ ID NO : 382), Figure 384 (SEQ ID NO : 384), Figure 386 (SEQ ID NO : 386), Figure 388 (SEQ ID NO : 388), Figure 390 (SEQ ID NO : 390), Figure 392 (SEQ ID NO : 392), Figure 394 (SEQ ID NO : 394), Figure 396 (SEQ ID NO : 396), Figure (SEQ ID NO : 398), Figure 400 (SEQ ID NO : 400), Figure 402 (SEQ ID NO : 402), Figure 404 (SEQ ID NO : 404), Figure 406 (SEQ ID NO : 406), Figure 408 (SEQ ID NO : 408), Figure 410 (SEQ ID NO : 410), Figure 412 (SEQ ID NO : 412), Figure 414 (SEQ ID NO : 414), Figure 416 (SEQ ID NO : 416), Figure 418 (SEQ ID NO : 418), Figure 420 (SEQ ID NO : 420), Figure 422 (SEQ ID NO : 422), Figure 424 (SEQ ID NO : 424), Figure 426 (SEQ ID NO : 426), Figure 428 (SEQ ID NO : 428), Figure 430 (SEQ ID NO : 430), Figure 432 (SEQ ID NO : 432), Figure 434 (SEQ ID NO : 434), Figure 436 (SEQ ID NO : 436), Figure 438 (SEQ ID NO : 438), Figure 440 (SEQ ID NO : 440), Figure 442 (SEQ ID NO : 442), Figure 444 (SEQ ID NO : 444), Figure 446 (SEQ ID NO : 446), Figure 448 (SEQ ID NO : 448),

Figure 450 (SEQ ID NO : 450), Figure 452 (SEQ ID NO : 452), Figure 454 (SEQ ID NO : 454), Figure 456 (SEQ ID NO : 456), Figure 458 (SEQ ID NO : Figure 460 (SEQ ID NO : 460), Figure 462 (SEQ ID NO : 462), Figure 464 (SEQ ID NO : 464), Figure 466 (SEQ ID NO : 466), Figure 468 (SEQ ID NO : 468), Figure 470 (SEQ ID NO : 470), Figure 472 (SEQ ID NO : 472), Figure 474 (SEQ ID NO : 474), Figure 476 (SEQ ID NO : 476), Figure 478 (SEQ ID NO : 478), Figure 480 (SEQ ID NO : 480), Figure 482 (SEQ ID NO : Figure 484 (SEQ ID NO : 484), Figure 486 (SEQ ID NO : 486), Figure 488 (SEQ ID NO : 488), Figure 490 (SEQ ID NO : 490), Figure 492 (SEQ ID NO : 492), Figure 494 (SEQ ID NO : 494), Figure 496 (SEQ ID NO : 496), Figure (SEQ ID NO : 498), Figure 500 (SEQ ID NO : 500), Figure 502 (SEQ ID NO : 502), Figure 504 (SEQ ID NO : 504), Figure 506 (SEQ ID NO : 506), Figure 508 (SEQ ID NO : 508), Figure 510 (SEQ ID NO : 510), Figure 512 (SEQ ID NO : 512), Figure 514 (SEQ ID NO : 514), Figure 516 (SEQ ID NO : 516), Figure 518 (SEQ ID NO : 518), Figure 520 (SEQ ID NO : 520), Figure 522 (SEQ ID NO : 522), Figure 524 (SEQ ID NO : 524), Figure 526 (SEQ ID NO : 526), Figure 528 (SEQ ID NO : 528), Figure 530 (SEQ ID NO : 530), Figure 532 (SEQ ID NO : 532), Figure 534 (SEQ ID NO : 534), Figure 536 (SEQ ID NO : 536), Figure 538 (SEQ ID NO : 538), Figure 540 (SEQ ID NO : 540), Figure 542 (SEQ ID NO : 542), Figure 544 (SEQ ID NO : 544), Figure 546 (SEQ ID NO : 546), Figure 548 (SEQ ID NO : 548), Figure 550 (SEQ ID NO : 550), Figure 552 (SEQ ID NO : 552), Figure 554 (SEQ ID NO : 554), Figure 556 (SEQ ID NO : 556), Figure 558 (SEQ ID NO : 558), Figure 560 (SEQ ID NO : 560), Figure 562 (SEQ ID NO : 562), Figure 564 (SEQ ID NO : 564), Figure 566 (SEQ ID NO : 566), Figure 568 (SEQ ID NO : 568), Figure 570 (SEQ ID NO : 570), Figure 572 (SEQ ID NO : 572), Figure 574 (SEQ ID NO : 574), Figure 576 (SEQ ID NO : 576), Figure 578 (SEQ ID NO : 578), Figure 580 (SEQ ID NO : 580), Figure 582 (SEQ ID NO : 582), Figure 584 (SEQ ID NO : 584), Figure 586 (SEQ ID NO : 586), Figure 588 (SEQ ID NO : Figure 590 (SEQ ID NO : 590), Figure 592 (SEQ ID NO : 592), Figure 594 (SEQ ID NO : 594), Figure 596 (SEQ ID NO : 596), Figure 598 (SEQ ID NO : 598), Figure 600 (SEQ ID NO : 600), Figure 602 (SEQ ID NO : 602), Figure 604 (SEQ ID NO : 604), Figure 606 (SEQ ID NO : 606), Figure 608 (SEQ ID NO : 608), and Figure 610 (SEQ ID NO : 610).

2. Isolated nucleic acid having at least 80 % nucleic acid sequence identity to a nucleotide sequence selected from the group consisting of the nucleotide sequence shown in Figure 1 (SEQ ID NO : 1), Figure 3 (SEQ ID NO : 3), Figure 5 (SEQ ID NO : Figure 7 (SEQ NO : 7), Figure 9 (SEQ NO : 9), Figure 11 (SEQ ID NO : Figure 13 (SEQ ID NO : 13), Figure 15 (SEQ ID NO : 15), Figure 17 (SEQ ID NO : 17), Figure 19 (SEQ NO : Figure 21 (SEQ ID NO : 21), Figure 23 (SEQ ID NO : 23), Figure 25 (SEQ ID NO : 25), Figure 27 (SEQ ID NO : 27), Figure 29 (SEQ ID NO : 29), Figure 31 (SEQ ID NO : 31), Figure 33 (SEQ ID NO : 33), Figure 35 (SEQ ID NO : 35), Figure 37 (SEQ ID NO : 37), Figure 39 (SEQ ID NO : 39), Figure 41 (SEQ ID NO : 41), Figure 43 (SEQ ID NO : 43), Figure 45 (SEQ ID NO : 45), Figure 47 (SEQ ID NO : 47), Figure 49 (SEQ ID NO : 49), Figure 51 (SEQ ID NO : 51), Figure 53 (SEQ ID NO : 53), Figure 55 (SEQ ID NO : 55), Figure 57 (SEQ NO : 57), Figure 59 (SEQ ID NO : 59), Figure 61 (SEQ ID NO : 61), Figure 63 (SEQ ID NO : 63), Figure 65 (SEQ ID NO : 65), Figure 67 (SEQ ID NO : 67), Figure 69 (SEQ ID NO : 69), Figure 71 : 71), Figure 73 (SEQ ID NO : 73), Figures 75A-75B (SEQ ID NO : 75), Figure 77 (SEQ ID NO : 77), Figure 79 (SEQ ID NO : 79), Figure (SEQ ID NO : 81), Figure 83 (SEQ ID NO : 83), Figure 85 : 85), Figure 87 (SEQ ID NO : 87), Figure 89 (SEQ ID NO : 89), Figure 91 (SEQ ID NO : 91), Figure 93 (SEQ ID NO : 93), Figure 95 (SEQ ID NO : 95), Figure 97 (SEQ ID NO : 97), Figure 99 (SEQ ID NO : 99), Figure 101 (SEQ ID NO : 101), Figure 103 (SEQ ID NO : 103), Figure 105 (SEQ ID NO : 105), Figure 107 (SEQ ID NO : 107), Figure 109 (SEQ ID NO : 109), Figure 111 (SEQ ID NO : Figure 113 (SEQ ID NO : 113), Figure 115 (SEQ ID NO : 115), Figure 117 (SEQ ID NO : 117), Figure 119 (SEQ ID NO : Figure 121 (SEQ ID NO : 121), Figure 123 (SEQ ID NO : 123), Figure 125 (SEQ ID NO : 125), Figure 127 (SEQ ID NO : 127), Figure 129 (SEQ ID NO : 129), Figure 131 (SEQ ID NO : Figure 133 (SEQ ID NO : 133), Figure 135 (SEQ ID NO : 135), Figure 137 (SEQ ID NO : 137), Figure 139 (SEQ ID NO : 139), Figure 141 (SEQ ID NO : Figure 143 (SEQ ID NO : 143), Figure 145 (SEQ ID NO : 145), Figure 147 (SEQ ID NO : Figure 149 (SEQ ID NO : 149), Figure 151 (SEQ ID NO : Figure 153 (SEQ ID NO : 153), Figure 155 (SEQ ID

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3. Isolated nucleic acid having at least 80 % nucleic acid sequence identity to a nucleotide sequence selected from the group consisting of the full-length coding sequence of the nucleotide sequence shown in Figure 1 (SEQ ID NO : 1), Figure 3 : 3), Figure 5 (SEQ ID NO : Figure 7 (SEQ ID NO : 7), Figure 9 (SEQ ID NO : 9), Figure NO : Figure 13 (SEQ ID NO : 13), Figure 15 : 15), Figure 17 (SEQ ID NO : 17), Figure 19 (SEQ ID NO : Figure 21 (SEQ ID NO : 21), Figure 23 (SEQ ID NO : 23), Figure 25 (SEQ ID NO : 25), Figure 27 (SEQ ID NO : 27), Figure 29 (SEQ ID NO : 29), Figure 31 (SEQ ID NO : 31), Figure 33 (SEQ ID NO : 33), Figure 35 (SEQ ID NO : 35), Figure 37 (SEQ ID NO : 37), Figure 39 (SEQ ID NO : 39), Figure 41 (SEQ NO : 41), Figure 43 (SEQ ID NO : 43), Figure 45 (SEQ ID NO : 45), Figure 47 (SEQ ID NO : 47), Figure 49 (SEQ ID NO : 49), Figure 51 (SEQ ID NO : 51), Figure 53 (SEQ ID NO : 53), Figure 55 (SEQ ID NO : 55), Figure 57 (SEQ ID NO : 57), Figure 59 (SEQ ID NO : 59), Figure 61 (SEQ ID NO : 61), Figure 63 (SEQ ID NO : 63), Figure 65 (SEQ ID NO : 65), Figure 67 (SEQ ID NO : 67), Figure 69 (SEQ ID NO : 69), Figure 71 (SEQ ID NO : 71), Figure 73 (SEQ ID : 73), Figures 75A-75B (SEQ ID : 75), Figure 77 (SEQ ID : 77), Figure 79 (SEQ ID : 79), Figure 81 : 81), Figure 83 (SEQ ID NO : 83), Figure 85 (SEQ ID : 85), Figure 87 (SEQ ID : Figure 89 (SEQ : 89), Figure 91 (SEQ ID NO : 91), Figure 93 (SEQ ID NO : 93), Figure 95 (SEQ ID NO : 95), Figure 97 (SEQ ID NO : 97), Figure 99 : 99), Figure 101 (SEQ ID NO : 101), Figure 103 (SEQ ID NO : 103), Figure 105 (SEQ ID NO : 105), Figure 107 (SEQ ID : 107), Figure 109 (SEQ ID NO : 109), Figure 111 (SEQ ID NO : 111), Figure 113 (SEQ ID : 113), Figure 115 (SEQ ID NO : 115), Figure 117 (SEQ ID NO : 117), Figure 119 (SEQ ID NO : Figure 121 (SEQ ID : 121), Figure 123 (SEQ ID : 123), Figure 125 (SEQ ID : 125), Figure 127 (SEQ ID NO : 127), Figure 129 (SEQ ID NO : 129), Figure 131 (SEQ ID NO : Figure 133 (SEQ ID NO : 133), Figure 135 (SEQ ID : 135), Figure 137 (SEQ ID : 137), Figure 139 (SEQ ID : 139), Figure 141 (SEQ ID : Figure 143 (SEQ ID : 143), Figure 145 (SEQ ID NO : 145), Figure 147 (SEQ ID : 147), Figure 149 (SEQ ID : 149), Figure (SEQ ID NO : Figure 153 (SEQ ID NO : 153), Figure 155 (SEQ ID NO : 155), Figure 157 (SEQ ID : 157), Figure 159 (SEQ ID NO : 159), Figure 161 (SEQ ID NO : 161), Figure 163 (SEQ ID NO : 163), Figure 165 (SEQ ID : 165), Figure 167 (SEQ ID : 167), Figure 169 (SEQ ID NO : 169), Figure 171 (SEQ ID : Figure 173 (SEQ ID NO : 173), Figure 175 (SEQ ID NO : 175), Figure 177 (SEQ ID NO : 177), Figure 179 (SEQ ID : 179), Figure 181 (SEQ ID NO : Figure 183 (SEQ ID NO : 183), Figure 185 (SEQ ID NO : 185), Figure 187 (SEQ ID NO : 187), Figure 189 (SEQ ID NO : 189), Figure 191 (SEQ ID NO : Figure 193 (SEQ ID NO : 193), Figure 195 (SEQ ID NO : 195), Figure 197 (SEQ ID NO : 197), Figure 199 (SEQ ID NO : Figure 201

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4. Isolated nucleic acid having at least 80 % nucleic acid sequence identity to the full-length coding sequence of the DNA deposited under any ATCC accession number shown in Table 7.

5. A vector comprising the nucleic acid of Claim

6. A host cell comprising the vector of Claim 5.

7. The host cell of Claim 6, wherein said cell is a CHO cell.

8. The host cell of Claim 6, wherein said cell is an E. coli.

9. The host cell of Claim 6, wherein said cell is a yeast cell.

10. A process for producing a PRO polypeptide comprising culturing the host cell of Claim 6 under conditions suitable for expression of said PRO polypeptide and recovering said PRO polypeptide from the cell culture.

11. An isolated polypeptide having at least 80% amino acid sequence identity to an amino acid sequence selected from the group consisting of the amino acid sequence shown in Figure 2 (SEQ ID NO : 2), Figure 4 (SEQ ID NO : 4), Figure 6 (SEQ ID NO : 6), Figure 8 (SEQ ID NO : 8), Figure 10 (SEQ ID NO : 10), Figure 12 (SEQ ID NO : 12), Figure 14 (SEQ ID NO : 14), Figure 16 (SEQ ID NO : Figure 18 (SEQ ID NO : 18), Figure 20 (SEQ ID NO : 20), Figure 22 (SEQ ID NO : 22), Figure 24 : 24), Figure 26 (SEQ ID NO : 26), Figure 28 (SEQ ID NO : 28), Figure 30 (SEQ ID NO : 30), Figure 32 (SEQ ID NO : 32), Figure 34 (SEQ ID NO : 34), Figure 36 (SEQ ID NO : 36), Figure 38 (SEQ ID NO : 38), Figure 40 (SEQ ID NO : Figure 42 (SEQ ID NO : 42), Figure 44 (SEQ ID NO : 44), Figure 46 (SEQ ID NO : 46), Figure 48 (SEQ ID NO : 48), Figure 50 (SEQ ID NO : 50), Figure 52 (SEQ ID NO : 52), Figure 54 (SEQ ID NO : 54), Figure 56 (SEQ ID NO : 56), Figure 58 (SEQ ID NO : Figure 60 (SEQ ID NO : 60), Figure 62 (SEQ ID NO : 62), Figure 64 (SEQ ID NO : 64), Figure 66 (SEQ ID NO : 66), Figure 68 (SEQ ID NO : 68), Figure 70 (SEQ ID NO : 70), Figure 72 (SEQ ID NO : 72), Figure 74 (SEQ ID NO : 74), Figure 76 (SEQ ID NO : 76), Figure 78 (SEQ ID NO : 78), Figure 80 (SEQ ID NO : 80), Figure 82 (SEQ ID NO : 82), Figure (SEQ ID NO : 84), Figure 86 (SEQ ID NO : 86), Figure 88 (SEQ ID NO : Figure 90 (SEQ ID NO : 90), Figure 92 (SEQ ID NO : 92), Figure 94 (SEQ ID NO : 94), Figure 96 (SEQ ID NO : 96), Figure 98 (SEQ ID NO : 98), Figure 100 (SEQ ID NO : 100), Figure 102 (SEQ ID NO : 102), Figure 104 (SEQ ID NO : 104), Figure 106 (SEQ ID NO : 106), Figure (SEQ ID NO : 108), Figure 110 (SEQ ID NO : 110), Figure 112 (SEQ ID NO : 112), Figure 114 (SEQ ID NO : 114), Figure 116 (SEQ ID NO : 116), Figure (SEQ ID NO : 118), Figure 120 (SEQ ID NO : 120),

Figure 122 (SEQ ID NO : 122), Figure 124 (SEQ ID NO : 124), Figure 126 (SEQ ID NO : 126), Figure 128 (SEQ ID NO : 128), Figure 130 (SEQ ID NO : 130), Figure 132 (SEQ ID NO : 132), Figure 134 (SEQ ID NO : 134), Figure 136 (SEQ ID NO : 136), Figure 138 (SEQ ID NO : 138), Figure 140 (SEQ ID NO : 140), Figure 142 (SEQ ID NO : 142), Figure 144 (SEQ ID NO : 144), Figure 146 (SEQ ID NO : 146), Figure 148 (SEQ ID NO : 148), Figure 150 (SEQ ID NO : 150), Figure 152 (SEQ ID NO : 152), Figure 154 (SEQ ID NO : 154), Figure 156 (SEQ ID NO : 156), Figure 158 (SEQ ID NO : 158), Figure 160 (SEQ ID NO : 160), Figure 162 (SEQ ID NO : 162), Figure 164 (SEQ ID NO : 164), Figure 166 (SEQ ID NO : 166), Figure 168 (SEQ ID NO : 168), Figure 170 (SEQ ID NO : 170), Figure 172 (SEQ ID NO : 172), Figure 174 (SEQ ID NO : 174), Figure 176 (SEQ ID NO : 176), Figure 178 (SEQ ID NO : 178), Figure 180 (SEQ ID NO : 180), Figure 182 (SEQ ID NO : 182), Figure 184 (SEQ ID NO : 184), Figure 186 (SEQ ID NO : 186), Figure 188 (SEQ ID NO : 188), Figure 190 (SEQ ID NO : Figure 192 (SEQ ID NO : 192), Figure 194 (SEQ ID NO : 194), Figure 196 (SEQ ID NO : 196), Figure 198 (SEQ ID NO : 198), Figure 200 (SEQ ID NO : 200), Figure 202 (SEQ ID NO : 202), Figure 204 (SEQ ID NO : 204), Figure 206 (SEQ ID NO : 206), Figure 208 (SEQ ID NO : 208), Figure 210 (SEQ ID NO : 210), Figure 212 (SEQ ID NO : 212), Figure 214 (SEQ ID NO : 214), Figure 216 (SEQ ID NO : 216), Figure 218 (SEQ ID NO : 218), Figure 220 (SEQ ID NO : 220), Figure 222 (SEQ ID NO : 222), Figure 224 (SEQ ID NO : 224), Figure 226 (SEQ ID NO : 226), Figure (SEQ ID NO : 228), Figure 230 (SEQ ID NO : 230), Figure 232 (SEQ ID NO : 232), Figure 234 (SEQ ID NO : 234), Figure 236 (SEQ ID NO : 236), Figure 238 (SEQ ID NO : 238), Figure 240 (SEQ ID NO : 240), Figure 242 (SEQ ID NO : 242), Figure 244 (SEQ ID NO : 244), Figure 246 (SEQ ID NO : 246), Figure (SEQ ID NO : Figure 250 (SEQ ID NO : 250), Figure 252 (SEQ ID NO : 252), Figure 254 (SEQ ID NO : 254), Figure 256 (SEQ ID NO : 256), Figure 258 (SEQ ID NO : 258), Figure 260 (SEQ ID NO : 260), Figure 262 (SEQ ID NO : 262), Figure 264 (SEQ ID NO : 264), Figure 266 (SEQ ID NO : 266), Figure 268 (SEQ ID NO : 268), Figure 270 (SEQ ID NO : 270), Figure 272 (SEQ ID NO : 272), Figure 274 (SEQ ID NO : 274), Figure 276 (SEQ ID NO : 276), Figure 278 (SEQ ID NO : 278), Figure 280 (SEQ ID NO : 280), Figure 282 (SEQ ID NO : 282), Figure 284 (SEQ ID NO : 284), Figure 286 (SEQ ID NO : 286), Figure 288 (SEQ ID NO : 288), Figure 290 (SEQ ID NO : 290), Figure 292 (SEQ ID NO : 292), Figure 294 (SEQ ID NO : 294), Figure 296 (SEQ ID NO : 296), Figure 298 (SEQ ID NO : 298), Figure 300 (SEQ ID NO : 300), Figure 302 (SEQ ID NO : 302), Figure 304 (SEQ ID NO : 304), Figure 306 (SEQ ID NO : 306), Figure 308 (SEQ ID NO : 308), Figure 310 (SEQ ID NO : 310), Figure 312 (SEQ ID NO : 312), Figure 314 (SEQ ID NO : 314), Figure 316 (SEQ ID NO : 316), Figure (SEQ ID NO : Figure 320 (SEQ ID NO : 320), Figure 322 (SEQ ID NO : 322), Figure 324 (SEQ ID NO : 324), Figure 326 (SEQ ID NO : 326), Figure (SEQ ID NO : 328), Figure 330 (SEQ ID NO : 330), Figure 332 (SEQ ID NO : 332), Figure 334 (SEQ ID NO : 334), Figure 336 (SEQ ID NO : 336), Figure 338 (SEQ ID NO : Figure 340 (SEQ ID NO : 340), Figure 342 (SEQ ID NO : 342), Figure 344 (SEQ ID NO : 344), Figure 346 (SEQ ID NO : 346), Figure 348 (SEQ ID NO : Figure 350 (SEQ ID NO : 350), Figure 352 (SEQ ID NO : 352), Figure 354 (SEQ ID Figure 356 (SEQ ID NO : 356), Figure (SEQ ID NO : 358), Figure 360 (SEQ ID NO : 360), Figure 362 (SEQ ID NO : 362), Figure 364 (SEQ ID NO : 364), Figure 366 (SEQ ID NO : 366), Figure 368 (SEQ ID NO : 368), Figure 370 (SEQ ID NO : 370), Figure 372 (SEQ ID NO : 372), Figure 374 (SEQ ID NO : 374), Figure 376 (SEQ ID NO : 376), Figure 378 (SEQ ID NO : 378), Figure 380 (SEQ ID NO : 380), Figure 382 (SEQ ID NO : Figure 384 (SEQ ID NO : 384), Figure 386 (SEQ ID NO : 386), Figure 388 (SEQ ID NO : 388), Figure 390 (SEQ ID NO : 390), Figure 392 (SEQ ID NO : 392), Figure 394 (SEQ ID NO : 394), Figure 396 (SEQ ID NO : 396), Figure 398 (SEQ ID NO : 398), Figure 400 (SEQ ID NO : 400), Figure 402 (SEQ ID NO : 402), Figure 404 (SEQ ID NO : 404), Figure 406 (SEQ ID NO : 406), Figure 408 (SEQ ID NO : 408), Figure 410 (SEQ ID NO : 410), Figure 412 (SEQ ID NO : 412), Figure 414 (SEQ ID NO : 414), Figure 416 (SEQ ID NO : 416), Figure 418 (SEQ ID NO : 418), Figure 420 (SEQ ID NO : 420), Figure 422 (SEQ ID NO : 422), Figure 424 (SEQ ID NO : 424), Figure 426 (SEQ ID NO : 426), Figure 428 (SEQ ID NO : 428), Figure 430 (SEQ ID NO : 430), Figure 432 (SEQ ID NO : 432), Figure 434 (SEQ ID NO : 434), Figure 436 (SEQ ID NO : 436), Figure 438 (SEQ ID NO : 438), Figure 440 (SEQ ID NO : 440), Figure 442 (SEQ ID NO : 442), Figure 444 (SEQ ID NO : 444), Figure 446 (SEQ ID NO : 446), Figure 448 (SEQ

ID NO : 448), Figure 450 (SEQ ID NO : 450), Figure 452 (SEQ ID NO : 452), Figure 454 (SEQ ID NO : 454), Figure 456 (SEQ ID NO : 456), Figure 458 (SEQ ID NO : 458), Figure 460 (SEQ ID NO : 460), Figure 462 (SEQ ID NO : 462), Figure 464 (SEQ ID NO : 464), Figure 466 (SEQ ID NO : 466), Figure 468 (SEQ ID NO : Figure 470 (SEQ ID NO : 470), Figure 472 (SEQ ID NO : 472), Figure 474 (SEQ ID NO : 474), Figure 476 (SEQ ID NO : 476), Figure 478 (SEQ ID NO : 478), Figure 480 (SEQ ID NO : 480), Figure 482 (SEQ ID NO : 482), Figure 484 (SEQ ID NO : Figure 486 (SEQ ID NO : 486), Figure (SEQ ID NO : Figure 490 (SEQ ID NO : 490), Figure 492 (SEQ ID NO : 492), Figure 494 (SEQ ID NO : 494), Figure 496 (SEQ ID NO : 496), Figure 498 (SEQ ID NO : Figure 500 (SEQ ID NO : 500), Figure 502 (SEQ ID NO : 502), Figure 504 (SEQ ID NO : 504), Figure 506 (SEQ ID NO : 506), Figure 508 (SEQ ID NO : 508), Figure 510 (SEQ ID NO : 510), Figure 512 (SEQ ID NO : 512), Figure 514 (SEQ ID NO : 514), Figure 516 (SEQ ID NO : 516), Figure 518 (SEQ ID NO : 518), Figure 520 (SEQ ID NO : 520), Figure 522 (SEQ ID NO : 522), Figure 524 (SEQ ID NO : 524), Figure 526 (SEQ ID NO : 526), Figure 528 (SEQ ID NO : 528), Figure 530 (SEQ ID NO : 530), Figure 532 (SEQ ID NO : 532), Figure 534 (SEQ ID NO : 534), Figure 536 (SEQ ID NO : 536), Figure 538 (SEQ ID NO : Figure 540 (SEQ ID NO : 540), Figure 542 (SEQ ID NO : 542), Figure 544 (SEQ ID NO : 544), Figure 546 (SEQ ID NO : 546), Figure 548 (SEQ ID NO : 548), Figure 550 (SEQ ID NO : 550), Figure 552 (SEQ ID NO : 552), Figure 554 (SEQ ID NO : 554), Figure 556 (SEQ ID NO : 556), Figure 558 (SEQ ID NO : 558), Figure 560 (SEQ ID NO : 560), Figure 562 (SEQ ID NO : 562), Figure 564 (SEQ ID NO : 564), Figure 566 (SEQ ID NO : 566), Figure 568 (SEQ ID NO : 568), Figure 570 (SEQ ID NO : 570), Figure 572 (SEQ ID NO : 572), Figure 574 (SEQ ID NO : 574), Figure 576 (SEQ ID NO : 576), Figure 578 (SEQ ID NO : 578), Figure 580 (SEQ ID NO : 580), Figure 582 (SEQ ID NO : 582), Figure 584 (SEQ ID NO : 584), Figure 586 (SEQ ID NO : Figure 588 (SEQ ID NO : Figure 590 (SEQ ID NO : 590), Figure 592 (SEQ ID NO : 592), Figure 594 (SEQ ID NO : 594), Figure 596 (SEQ ID NO : 596), Figure 598 (SEQ ID NO : 598), Figure 600 (SEQ ID NO : 600), Figure 602 (SEQ ID NO : 602), Figure 604 (SEQ ID NO : 604), Figure 606 (SEQ ID NO : 606), Figure 608 (SEQ ID NO : 608), and Figure 610 (SEQ ID NO : 610).

12. An isolated polypeptide having at least 80% amino acid sequence identity to an amino acid sequence encoded by the full-length coding sequence of the DNA deposited under any ATCC accession number shown in Table 7.

13. A chimeric molecule comprising a polypeptide according to Claim 11 fused to a heterologous amino acid sequence.

14. The chimeric molecule of Claim 13, wherein said heterologous amino acid sequence is an epitope tag sequence.

15. The chimeric molecule of Claim 13, wherein said heterologous amino acid sequence is a Fc region of an immunoglobulin.

16. An antibody which specifically binds to a polypeptide according to Claim

17. The antibody of Claim 16, wherein said antibody is a monoclonal antibody, a humanized antibody or a single-chain antibody.

18. Isolated nucleic acid having at least nucleic acid sequence identity to : (a) a nucleotide sequence encoding the polypeptide shown in Figure 2 (SEQ ID NO : 2), Figure 4 (SEQ ID NO : 4), Figure 6 (SEQ ID NO : 6), Figure 8 (SEQ ID NO : 8), Figure 10 (SEQ ID NO : 10), Figure 12 (SEQ ID NO : 12), Figure 14 (SEQ ID NO : 14), Figure 16 (SEQ ID NO : 16), Figure 18 (SEQ ID NO : 18), Figure 20 (SEQ ID NO : 20), Figure 22 (SEQ ID NO : 22), Figure 24 (SEQ ID NO : 24), Figure 26 (SEQ ID NO :

26), Figure 28 (SEQ ID NO : 28), Figure 30 (SEQ ID NO : 30), Figure 32 (SEQ ID NO : 32), Figure 34 (SEQ ID NO : 34), Figure 36 (SEQ ID NO : 36), Figure 38 (SEQ ID NO : 38), Figure 40 (SEQ ID NO : 40), Figure 42 (SEQ ID NO : 42), Figure 44 (SEQ ID NO : 44), Figure 46 (SEQ ID NO : 46), Figure (SEQ ID NO : 48), Figure 50 (SEQ ID NO : 50), Figure 52 (SEQ ID NO : 52), Figure 54 (SEQ ID NO : 54), Figure 56 (SEQ ID NO : 56), Figure 58 (SEQ ID NO : 58), Figure 60 (SEQ ID NO : 60), Figure 62 (SEQ ID NO : 62), Figure 64 (SEQ ID NO : 64), Figure 66 (SEQ ID NO : 66), Figure 68 (SEQ ID NO : 68), Figure 70 (SEQ ID NO : 70), Figure 72 (SEQ ID NO : 72), Figure 74 (SEQ ID NO : 74), Figure 76 (SEQ ID NO : 76), Figure 78 (SEQ ID NO : 78), Figure 80 (SEQ ID NO : 80), Figure 82 (SEQ ID NO : 82), Figure 84 (SEQ ID NO : 84), Figure 86 (SEQ ID NO : 86), Figure 88 (SEQ ID NO : 88), Figure 90 (SEQ ID NO : 90), Figure 92 (SEQ ID NO : 92), Figure 94 (SEQ ID NO : 94), Figure 96 (SEQ ID NO : 96), Figure 98 (SEQ ID NO : 98), Figure 100 (SEQ ID NO : 100), Figure 102 (SEQ ID NO : 102), Figure 104 (SEQ ID NO : 104), Figure 106 (SEQ ID NO : 106), Figure 108 (SEQ ID NO : 108), Figure 110 (SEQ ID NO : 110), Figure 112 (SEQ ID NO : 112), Figure 114 (SEQ ID NO : 114), Figure 116 (SEQ ID NO : 116), Figure 118 (SEQ ID NO : 118), Figure 120 (SEQ ID NO : 120), Figure 122 (SEQ ID NO : 122), Figure 124 (SEQ ID NO : 124), Figure 126 (SEQ ID NO : 126), Figure 128 (SEQ ID NO : 128), Figure 130 (SEQ ID NO : 130), Figure 132 (SEQ ID NO : 132), Figure 134 (SEQ ID NO : 134), Figure 136 (SEQ ID NO : 136), Figure 138 (SEQ ID NO : 138), Figure 140 (SEQ ID NO : 140), Figure 142 (SEQ ID NO : 142), Figure 144 (SEQ ID NO : 144), Figure 146 (SEQ ID NO : 146), Figure 148 (SEQ ID NO : 148), Figure 150 (SEQ ID NO : 150), Figure 152 (SEQ ID NO : 152), Figure 154 (SEQ ID NO : 154), Figure 156 (SEQ ID NO : 156), Figure 158 (SEQ ID NO : 158), Figure 160 (SEQ ID NO : 160), Figure 162 (SEQ ID NO : 162), Figure 164 (SEQ ID NO : 164), Figure 166 (SEQ ID NO : 166), Figure 168 (SEQ ID NO : 168), Figure 170 (SEQ ID NO : 170), Figure 172 (SEQ ID NO : 172), Figure 174 (SEQ ID NO : 174), Figure 176 (SEQ ID NO : 176), Figure 178 (SEQ ID NO : 178), Figure (SEQ ID NO : 180), Figure 182 (SEQ ID NO : 182), Figure 184 (SEQ ID NO : 184), Figure 186 (SEQ ID NO : 186), Figure 188 (SEQ ID NO : Figure 190 (SEQ ID NO : Figure 192 (SEQ ID NO : 192), Figure 194 (SEQ ID NO : 194), Figure 196 (SEQ ID NO : 196), Figure 198 (SEQ ID NO : 198), Figure 200 (SEQ ID NO : 200), Figure 202 (SEQ ID NO : 202), Figure 204 (SEQ ID NO : 204), Figure 206 (SEQ ID NO : 206), Figure 208 (SEQ ID NO : 208), Figure 210 (SEQ ID NO : 210), Figure 212 (SEQ ID NO : 212), Figure 214 (SEQ ID NO : 214), Figure 216 (SEQ ID NO : 216), Figure 218 (SEQ ID NO : 218), Figure 220 (SEQ ID NO : 220), Figure 222 (SEQ ID NO : 222), Figure 224 (SEQ ID NO : 224), Figure 226 (SEQ ID NO : 226), Figure 228 (SEQ ID NO : 228), Figure 230 (SEQ ID NO : 230), Figure 232 (SEQ ID NO : 232), Figure 234 (SEQ ID NO : 234), Figure 236 (SEQ ID NO : 236), Figure (SEQ ID NO : 238), Figure 240 (SEQ ID NO : 240), Figure 242 (SEQ ID NO : 242), Figure 244 (SEQ ID NO : 244), Figure 246 (SEQ ID NO : 246), Figure 248 (SEQ ID NO : 248), Figure 250 (SEQ ID NO : 250), Figure 252 (SEQ ID NO : 252), Figure 254 (SEQ ID NO : 254), Figure 256 (SEQ ID NO : 256), Figure 258 (SEQ ID NO : 258), Figure 260 (SEQ ID NO : 260), Figure 262 (SEQ ID NO : 262), Figure 264 (SEQ ID NO : 264), Figure 266 (SEQ ID NO : Figure 268 (SEQ ID NO : 268), Figure 270 (SEQ ID NO : 270), Figure 272 (SEQ ID NO : 272), Figure 274 (SEQ ID NO : 274), Figure 276 (SEQ ID NO : 276), Figure 278 (SEQ ID NO : 278), Figure 280 (SEQ ID NO : 280), Figure 282 (SEQ ID NO : 282), Figure 284 (SEQ ID NO : 284), Figure (SEQ ID NO : 286), Figure 288 (SEQ ID NO : 288), Figure 290 (SEQ ID NO : 290), Figure 292 (SEQ ID NO : 292), Figure 294 (SEQ ID NO : 294), Figure 296 (SEQ ID NO : 296), Figure 298 (SEQ ID NO : 298), Figure 300 (SEQ ID NO : 300), Figure 302 (SEQ ID NO : 302), Figure 304 (SEQ ID NO : 304), Figure 306 (SEQ ID NO : 306), Figure 308 (SEQ ID NO : 308), Figure 310 (SEQ ID NO : 310), Figure 312 (SEQ ID NO : 312), Figure 314 (SEQ ID NO : 314), Figure 316 (SEQ ID NO : 316), Figure 318 (SEQ ID NO : 318), Figure 320 (SEQ ID NO : 320), Figure 322 (SEQ ID NO : 322), Figure 324 (SEQ ID NO : 324), Figure 326 (SEQ ID NO : 326), Figure (SEQ ID NO : 328), Figure 330 (SEQ ID NO : 330), Figure 332 (SEQ ID NO : 332), Figure 334 (SEQ ID NO : 334), Figure 336 (SEQ ID NO : 336), Figure 338 (SEQ ID NO : 338), Figure 340 (SEQ ID NO : 340), Figure 342 (SEQ ID NO : 342), Figure 344 (SEQ ID NO : 344), Figure 346 (SEQ ID NO : 346), Figure 348 (SEQ ID NO : Figure 350 (SEQ ID NO : 350), Figure 352 (SEQ ID NO : 352), Figure 354 (SEQ ID NO : 354), Figure 356 (SEQ ID NO : 356), Figure 358 (SEQ ID NO :

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74), Figure 76 (SEQ ID NO : 76), Figure 78 (SEQ ID NO : 78), Figure 80 (SEQ ID NO : 80), Figure 82 (SEQ ID NO : 82), Figure 84 (SEQ ID NO : 84), Figure 86 (SEQ ID NO : 86), Figure (SEQ ID NO : 88), Figure 90 (SEQ ID NO : 90), Figure 92 (SEQ ID NO : 92), Figure 94 (SEQ ID NO : 94), Figure 96 (SEQ ID NO : 96), Figure 98 (SEQ ID NO : 98), Figure 100 (SEQ ID NO : 100), Figure 102 (SEQ ID NO : 102), Figure 104 (SEQ ID NO : 104), Figure 106 (SEQ ID NO : 106), Figure 108 (SEQ ID NO : 108), Figure 110 (SEQ ID NO : 110), Figure 112 (SEQ ID NO : 112), Figure 114 (SEQ ID NO : 114), Figure 116 (SEQ ID NO : 116), Figure 118 (SEQ ID NO : Figure 120 (SEQ ID NO : 120), Figure 122 (SEQ ID : 122), Figure 124 (SEQ ID : 124), Figure 126 (SEQ ID NO : 126), Figure 128 (SEQ ID : 128), Figure 130 (SEQ ID : 130), Figure 132 (SEQ ID : 132), Figure 134 (SEQ ID NO : 134), Figure 136 (SEQ ID : 136), Figure (SEQ ID : 138), Figure 140 (SEQ ID NO : 140), Figure 142 (SEQ ID : 142), Figure 144 (SEQ ID NO : 144), Figure 146 (SEQ ID NO : 146), Figure 148 (SEQ ID NO : 148), Figure 150 (SEQ ID NO : 150), Figure 152 (SEQ ID : 152), Figure 154 (SEQ ID : 154), Figure 156 (SEQ ID NO : 156), Figure 158 (SEQ ID : 158), Figure 160 (SEQ ID : 160), Figure 162 (SEQ ID : 162), Figure 164 (SEQ ID : 164), Figure 166 (SEQ ID NO : 166), Figure 168 (SEQ ID : 168), Figure 170 (SEQ ID : 170), Figure 172 (SEQ ID : 172), Figure 174 (SEQ ID : 174), Figure 176 (SEQ ID : 176), Figure 178 (SEQ ID NO : 178), Figure 180 (SEQ ID : 180), Figure 182 (SEQ ID NO : 182), Figure 184 (SEQ ID NO : 184), Figure 186 (SEQ ID NO : 186), Figure 188 (SEQ ID NO : 188), Figure 190 (SEQ ID NO : Figure 192 (SEQ ID : 192), Figure 194 (SEQ ID : 194), Figure 196 (SEQ ID : 196), Figure 198 (SEQ ID : 198), Figure 200 (SEQ ID : 200), Figure 202 (SEQ ID : 202), Figure 204 (SEQ ID : 204), Figure 206 (SEQ ID : 206), Figure (SEQ ID : 208), Figure 210 (SEQ ID NO : 210), Figure 212 (SEQ ID NO : 212), Figure 214 (SEQ ID : 214), Figure 216 (SEQ ID NO : 216), Figure 218 (SEQ ID NO : 218), Figure 220 (SEQ ID NO : 220), Figure 222 (SEQ ID NO : 222), Figure 224 (SEQ ID NO : 224), Figure 226 (SEQ ID NO : 226), Figure 228 (SEQ ID NO : 228), Figure 230 (SEQ ID NO : 230), Figure 232 (SEQ ID NO : 232), Figure 234 (SEQ ID NO : 234), Figure 236 (SEQ ID NO : 236), Figure 238 (SEQ ID NO : 238), Figure 240 (SEQ ID NO : 240), Figure 242 (SEQ ID NO : 242), Figure 244 (SEQ ID NO : 244), Figure 246 (SEQ ID NO : 246), Figure (SEQ ID NO : 248), (SEQ ID NO : 250), Figure 252 (SEQ ID NO : 252), Figure 254 (SEQ ID NO : 254), Figure 256 (SEQ ID NO : 256), Figure 258 (SEQ ID NO : 258), Figure 260 (SEQ ID NO : 260), Figure 262 (SEQ ID NO : 262), Figure 264 (SEQ ID NO : 264), Figure 266 (SEQ ID NO : 266), Figure 268 (SEQ ID NO : Figure 270 (SEQ ID NO : 270), Figure 272 (SEQ ID NO : 272), Figure 274 (SEQ ID NO : 274), Figure 276 (SEQ ID NO : 276), Figure 278 (SEQ ID NO : 278), Figure 280 (SEQ ID NO : 280), Figure 282 (SEQ ID NO : 282), Figure 284 (SEQ ID NO : Figure 286 (SEQ ID NO : 286), Figure 288 (SEQ ID NO : 288), Figure 290 (SEQ ID NO : 290), Figure 292 (SEQ ID NO : 292), Figure 294 (SEQ ID NO : 294), Figure 296 (SEQ ID NO : 296), Figure 298 (SEQ ID NO : 298), Figure 300 (SEQ ID NO : 300), Figure 302 (SEQ ID NO : 302), Figure 304 (SEQ ID NO : 304), Figure 306 (SEQ ID NO : 306), Figure 308 (SEQ ID NO : 308), Figure 310 (SEQ ID NO : Figure 312 (SEQ ID NO : 312), Figure 314 (SEQ ID NO : 314), Figure 316 (SEQ ID NO : 316), Figure 318 (SEQ ID NO : 318), Figure 320 (SEQ ID NO : 320), Figure 322 (SEQ ID NO : 322), Figure 324 (SEQ ID NO : 324), Figure 326 (SEQ ID NO : 326), Figure 328 (SEQ ID NO : 328), Figure 330 (SEQ ID NO : 330), Figure 332 (SEQ ID NO : 332), Figure 334 (SEQ ID NO : 334), Figure 336 (SEQ ID NO : 336), Figure 338 (SEQ ID NO : 338), Figure 340 (SEQ ID NO : 340), Figure 342 (SEQ ID NO : 342), Figure 344 (SEQ ID NO : 344), Figure 346 (SEQ ID NO : 346), Figure 348 (SEQ ID NO : 348), Figure 350 (SEQ ID NO : 350), Figure 352 (SEQ ID NO : 352), Figure 354 (SEQ ID NO : 354), Figure 356 (SEQ ID NO : 356), Figure 358 (SEQ ID NO : 358), Figure 360 (SEQ ID NO : 360), Figure 362 (SEQ ID NO : 362), Figure 364 (SEQ ID NO : 364), Figure 366 (SEQ ID NO : 366), Figure 368 (SEQ ID NO : 368), Figure 370 (SEQ ID NO : 370), Figure 372 (SEQ ID NO : 372), Figure 374 (SEQ ID NO : 374), Figure 376 (SEQ ID NO : 376), Figure 378 (SEQ ID NO : 378), Figure 380 (SEQ ID NO : 380), Figure 382 (SEQ ID NO : 382), Figure 384 (SEQ ID NO : 384), Figure 386 (SEQ ID NO : Figure 388 (SEQ ID NO : 388), Figure 390 (SEQ ID NO : 390), Figure 392 (SEQ ID NO : 392), Figure 394 (SEQ ID NO : 394), Figure 396 (SEQ ID NO : 396), Figure 398 (SEQ ID NO : 398), Figure 400 (SEQ ID NO : 400), Figure 402 (SEQ ID NO : 402), Figure 404 (SEQ ID NO : 404), Figure 406 (SEQ ID NO : 406), Figure (SEQ ID NO : 408), Figure 410 (SEQ ID NO : 410), Figure 412 (SEQ

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NO : 130), Figure 132 (SEQ ID NO : 132), Figure 134 (SEQ ID NO : 134), Figure 136 (SEQ ID NO : Figure 138 (SEQ ID NO : Figure 140 (SEQ ID NO : 140), Figure 142 (SEQ ID NO : 142), Figure 144 (SEQ ID NO : 144), Figure 146 (SEQ ID NO : 146), Figure 148 (SEQ ID NO : 148), Figure 150 (SEQ ID NO : Figure 152 (SEQ ID NO : 152), Figure 154 (SEQ ID NO : 154), Figure 156 (SEQ ID NO : 156), Figure 158 (SEQ ID NO : 158), Figure 160 (SEQ ID NO : 160), Figure 162 (SEQ ID NO : 162), Figure 164 (SEQ ID NO : 164), Figure 166 (SEQ ID NO : 166), Figure 168 (SEQ ID NO : 168), Figure 170 (SEQ ID NO : 170), Figure 172 (SEQ ID NO : 172), Figure 174 (SEQ ID NO : 174), Figure 176 (SEQ ID NO : 176), Figure 178 (SEQ ID NO : 178), Figure 180 (SEQ ID NO : 180), Figure 182 (SEQ ID NO : 182), Figure 184 (SEQ ID NO : 184), Figure 186 (SEQ ID NO : 186), Figure 188 (SEQ ID NO : 188), Figure 190 (SEQ ID NO : Figure 192 (SEQ ID NO : 192), Figure 194 (SEQ ID NO : 194), Figure 196 (SEQ ID NO : 196), Figure 198 (SEQ ID NO : 198), Figure 200 (SEQ ID NO : 200), Figure 202 (SEQ ID NO : 202), Figure 204 (SEQ ID NO : 204), Figure 206 (SEQ ID NO : 206), Figure 208 (SEQ ID NO : 208), Figure 210 (SEQ ID NO : Figure 212 (SEQ ID NO : 212), Figure 214 (SEQ ID NO : 214), Figure 216 (SEQ ID NO : 216), Figure 218 (SEQ NO : 218), Figure 220 (SEQ ID NO : 220), Figure 222 (SEQ ID NO : 222), Figure 224 (SEQ ID NO : 224), Figure 226 (SEQ ID NO : 226), Figure 228 (SEQ ID NO : 228), Figure 230 (SEQ ID NO : 230), Figure 232 (SEQ ID NO : 232), Figure 234 (SEQ ID NO : 234), Figure 236 (SEQ ID NO : 236), Figure 238 (SEQ ID NO : 238), Figure 240 (SEQ ID NO : 240), Figure 242 (SEQ ID NO : 242), Figure 244 (SEQ ID NO : 244), Figure 246 (SEQ ID NO : 246), Figure 248 (SEQ ID NO : 248), Figure 250 (SEQ ID NO : 250), Figure 252 (SEQ ID NO : 252), Figure 254 (SEQ ID NO : 254), Figure 256 (SEQ ID NO : 256), Figure 258 (SEQ ID NO : Figure 260 (SEQ ID NO : 260), Figure 262 (SEQ ID NO : 262), Figure 264 (SEQ ID NO : 264), Figure 266 (SEQ ID NO : 266), Figure 268 (SEQ ID NO : 268), Figure 270 (SEQ ID NO : 270), Figure 272 (SEQ ID NO : 272), Figure 274 (SEQ ID NO : 274), Figure 276 (SEQ ID NO : 276), Figure 278 (SEQ ID NO : 278), Figure 280 (SEQ ID NO : Figure 282 (SEQ ID NO : 282), Figure 284 (SEQ ID NO : 284), Figure (SEQ ID NO : 286), Figure (SEQ ID NO : 288), Figure 290 (SEQ ID NO : 290), Figure 292 (SEQ ID NO : 292), Figure 294 (SEQ ID NO : 294), Figure 296 (SEQ ID NO : 296), Figure (SEQ ID NO : 298), Figure 300 (SEQ ID NO : 300), Figure 302 (SEQ ID NO : 302), Figure 304 (SEQ ID NO : 304), Figure 306 (SEQ ID NO : 306), Figure 308 (SEQ ID NO : 308), Figure 310 (SEQ ID NO : 310), Figure 312 (SEQ ID NO : 312), Figure 314 (SEQ ID NO : 314), Figure 316 (SEQ ID NO : 316), Figure 318 (SEQ ID NO : 318), Figure 320 (SEQ ID NO : 320), Figure 322 (SEQ ID NO : 322), Figure 324 (SEQ ID NO : 324), Figure 326 (SEQ ID NO : 326), Figure 328 (SEQ ID NO : 328), Figure 330 (SEQ ID NO : 330), Figure 332 (SEQ ID NO : 332), Figure 334 (SEQ ID NO : 334), Figure 336 (SEQ ID NO : 336), Figure 338 (SEQ ID NO : 338), Figure 340 (SEQ ID NO : 340), Figure 342 (SEQ ID NO : 342), Figure 344 (SEQ ID NO : 344), Figure 346 (SEQ ID NO : 346), Figure 348 (SEQ ID NO : 348), Figure 350 (SEQ ID NO : 350), Figure 352 (SEQ ID NO : 352), Figure 354 (SEQ ID NO : 354), Figure 356 (SEQ ID NO : 356), Figure 358 (SEQ ID NO : 358), Figure 360 (SEQ ID NO : 360), Figure 362 (SEQ ID NO : 362), Figure 364 (SEQ ID NO : 364), Figure 366 (SEQ ID NO : 366), Figure 368 (SEQ ID NO : 368), Figure 370 (SEQ ID NO : 370), Figure 372 (SEQ ID NO : 372), Figure 374 (SEQ ID NO : 374), Figure 376 (SEQ ID NO : 376), Figure 378 (SEQ ID NO : 378), Figure 380 (SEQ ID NO : 380), Figure 382 (SEQ ID NO : 382), Figure 384 (SEQ ID NO : 384), Figure 386 (SEQ ID NO : 386), Figure 388 (SEQ ID NO : 388), Figure 390 (SEQ ID NO : 390), Figure 392 (SEQ ID NO : 392), Figure 394 (SEQ ID NO : 394), Figure 396 (SEQ ID NO : 396), Figure 398 (SEQ ID NO : 398), Figure 400 (SEQ ID NO : 400), Figure 402 (SEQ ID NO : 402), Figure 404 (SEQ ID NO : 404), Figure 406 (SEQ ID NO : 406), Figure (SEQ ID NO : 408), Figure 410 (SEQ ID NO : 410), Figure 412 (SEQ ID NO : 412), Figure 414 (SEQ ID NO : 414), Figure 416 (SEQ ID NO : 416), Figure 418 (SEQ ID NO : 418), Figure 420 (SEQ ID NO : 420), Figure 422 (SEQ ID NO : 422), Figure 424 (SEQ ID NO : 424), Figure 426 (SEQ ID NO : 426), Figure 428 (SEQ ID NO : 428), Figure 430 (SEQ ID NO : 430), Figure 432 (SEQ ID NO : 432), Figure 434 (SEQ ID NO : 434), Figure 436 (SEQ ID NO : 436), Figure 438 (SEQ ID NO : 438), Figure 440 (SEQ ID NO : 440), Figure 442 (SEQ ID NO : 442), Figure 444 (SEQ ID NO : 444), Figure 446 (SEQ ID NO : 446), Figure 448 (SEQ ID NO : 448), Figure 450 (SEQ ID NO : 450), Figure 452 (SEQ ID NO : 452), Figure 454 (SEQ ID NO : 454), Figure 456 (SEQ ID NO : 456),

Figure 458 (SEQ ID NO : 458), Figure 460 (SEQ ID NO : 460), Figure 462 (SEQ ID NO : 462), Figure 464 (SEQ ID NO : 464), Figure 466 (SEQ ID NO : 466), Figure 468 (SEQ ID NO : 468), Figure 470 (SEQ ID NO : 470), Figure 472 (SEQ ID NO : 472), Figure 474 (SEQ ID NO : 474), Figure 476 (SEQ ID NO : 476), Figure 478 (SEQ ID NO : 478), Figure 480 (SEQ ID NO : Figure 482 (SEQ ID NO : 482), Figure 484 (SEQ ID NO : 484), Figure 486 (SEQ ID NO : 486), Figure 488 (SEQ ID NO : 488), Figure 490 (SEQ ID NO : 490), Figure 492 (SEQ ID NO : 492), Figure 494 (SEQ ID NO : 494), Figure 496 (SEQ ID NO : 496), Figure 498 (SEQ ID NO : 498), Figure 500 (SEQ ID NO : 500), Figure 502 (SEQ ID NO : 502), Figure 504 (SEQ ID NO : 504), Figure 506 (SEQ ID NO : 506), Figure 508 (SEQ ID NO : 508), Figure 510 (SEQ ID NO : 510), Figure 512 (SEQ ID NO : 512), Figure 514 (SEQ ID NO : 514), Figure 516 (SEQ ID NO : 516), Figure 518 (SEQ ID NO : Figure 520 (SEQ ID NO : 520), Figure 522 (SEQ ID NO : 522), Figure 524 (SEQ ID NO : 524), Figure 526 (SEQ ID NO : 526), Figure (SEQ ID NO : 528), Figure 530 (SEQ ID NO : 530), Figure 532 (SEQ ID NO : 532), Figure 534 (SEQ ID NO : 534), Figure 536 (SEQ ID NO : 536), Figure 538 (SEQ ID NO : 538), Figure (SEQ ID NO : 540), Figure 542 (SEQ ID NO : 542), Figure 544 (SEQ ID NO : 544), Figure 546 (SEQ ID NO : 546), Figure 548 (SEQ ID NO : 548), Figure 550 (SEQ ID NO : 550), Figure 552 (SEQ ID NO : 552), Figure 554 (SEQ ID NO : 554), Figure 556 (SEQ ID NO : 556), Figure 558 (SEQ ID NO : Figure 560 (SEQ ID NO : 560), Figure 562 (SEQ ID NO : 562), Figure 564 (SEQ ID NO : 564), Figure 566 (SEQ ID NO : 566), Figure 568 (SEQ ID NO : 568), Figure 570 (SEQ ID NO : 570), Figure 572 (SEQ ID NO : 572), Figure 574 (SEQ ID NO : 574), Figure 576 (SEQ ID NO : 576), Figure 578 (SEQ ID NO : 578), Figure 580 (SEQ ID NO : 580), Figure 582 (SEQ ID NO : 582), Figure 584 (SEQ ID NO : 584), Figure 586 (SEQ ID NO : 586), Figure 588 (SEQ ID NO : 588), Figure 590 (SEQ NO : 590), Figure 592 (SEQ ID NO : 592), Figure 594 (SEQ ID NO : 594), Figure 596 (SEQ ID NO : 596), Figure 598 (SEQ ID NO : 598), Figure 600 (SEQ ID NO : 600), Figure 602 (SEQ ID NO : 602), Figure 604 (SEQ NO : 604), Figure 606 (SEQ ID NO : 606), Figure 608 (SEQ ID NO : 608), or Figure 610 (SEQ ID NO : 610), lacking its associated signal peptide.

19. An isolated polypeptide having at least 80% amino acid sequence identity to : (a) an amino acid sequence of the polypeptide shown in Figure 2 (SEQ ID NO : 2), Figure 4 (SEQ ID NO : 4), Figure 6 (SEQ ID NO : 6), Figure 8 (SEQ ID NO : 8), Figure 10 (SEQ ID NO : 10), Figure 12 (SEQ ID NO : 12), Figure 14 (SEQ ID NO : 14), Figure 16 (SEQ ID NO : 16), Figure 18 (SEQ ID NO : 18), Figure 20 (SEQ ID NO : 20), Figure 22 (SEQ ID NO : 22), Figure 24 (SEQ ID NO : 24), Figure 26 (SEQ ID NO : 26), Figure 28 (SEQ ID NO : Figure 30 (SEQ ID NO : 30), Figure 32 (SEQ ID NO : 32), Figure 34 (SEQ ID NO : 34), Figure 36 (SEQ ID NO : 36), Figure 38 (SEQ ID NO : 38), Figure 40 (SEQ ID NO : 40), Figure 42 (SEQ ID NO : 42), Figure 44 (SEQ ID NO : 44), Figure 46 (SEQ ID NO : 46), Figure 48 (SEQ ID NO : 48), Figure 50 (SEQ ID NO : 50), Figure 52 (SEQ ID NO : 52), Figure 54 (SEQ ID NO : 54), Figure 56 (SEQ ID NO : 56), Figure 58 (SEQ ID NO : 58), Figure 60 (SEQ ID NO : 60), Figure 62 (SEQ ID NO : 62), Figure 64 (SEQ ID NO : 64), Figure 66 (SEQ : 66), Figure 68 (SEQ ID NO : 68), Figure 70 (SEQ ID NO : 70), Figure 72 (SEQ ID NO : 72), Figure 74 (SEQ ID NO : 74), Figure 76 (SEQ ID NO : 76), Figure 78 (SEQ ID NO : 78), Figure 80 (SEQ ID NO : 80), Figure 82 (SEQ ID NO : 82), Figure 84 (SEQ ID NO : 84), Figure 86 (SEQ ID NO : 86), Figure 88 (SEQ ID NO : 88), Figure 90 (SEQ ID NO : 90), Figure 92 (SEQ ID NO : 92), Figure 94 (SEQ ID NO : 94), Figure 96 (SEQ ID NO : 96), Figure 98 (SEQ ID NO : 98), Figure 100 (SEQ ID NO : 100), Figure 102 (SEQ ID NO : 102), Figure 104 (SEQ ID NO : 104), Figure 106 (SEQ ID NO : 106), Figure 108 (SEQ ID NO : 108), Figure 110 (SEQ ID NO : 110), Figure 112 (SEQ ID NO : 112), Figure 114 (SEQ ID NO : 114), Figure (SEQ ID NO : 116), Figure 118 (SEQ ID NO : Figure 120 (SEQ ID NO : 120), Figure 122 (SEQ ID NO : 122), Figure 124 (SEQ ID NO : 124), Figure 126 (SEQ ID NO : 126), Figure 128 (SEQ ID NO : 128), Figure 130 (SEQ ID NO : 130), Figure 132 (SEQ ID NO : 132), Figure 134 (SEQ ID NO : 134), Figure 136 (SEQ ID NO : 136), Figure 138 (SEQ ID NO : 138), Figure 140 (SEQ ID NO : 140), Figure 142 (SEQ ID NO : 142), Figure 144 (SEQ ID NO : 144), Figure (SEQ ID NO : Figure (SEQ ID NO : 148), Figure (SEQ ID NO : 150), Figure 152 (SEQ ID NO : 152), Figure 154 (SEQ ID NO : 154), Figure 156 (SEQ ID NO : 156), Figure 158 (SEQ ID NO : 158), Figure 160 (SEQ ID NO : 160), Figure 162 (SEQ

ID NO : 162), Figure 164 (SEQ ID NO : 164), Figure 166 (SEQ ID NO : 166), Figure 168 (SEQ ID NO : 168), Figure 170 (SEQ ID NO : 170), Figure 172 (SEQ ID NO : 172), Figure 174 (SEQ ID NO : 174), Figure 176 (SEQ ID NO : 176), Figure 178 (SEQ ID NO : 178), Figure 180 (SEQ ID NO : 180), Figure 182 (SEQ : 182), Figure 184 (SEQ ID NO : 184), Figure 186 (SEQ ID NO : 186), Figure 188 (SEQ ID NO : Figure 190 (SEQ ID NO : Figure 192 (SEQ ID NO : 192), Figure 194 (SEQ ID NO : 194), Figure 196 (SEQ ID NO : 196), Figure 198 (SEQ ID NO : Figure 200 (SEQ ID NO : 200), Figure 202 (SEQ ID NO : 202), Figure 204 (SEQ ID NO : Figure 206 (SEQ ID NO : 206), Figure 208 (SEQ ID NO : 208), Figure 210 (SEQ ID NO : 210), Figure 212 (SEQ ID NO : 212), Figure 214 (SEQ ID NO : 214), Figure 216 (SEQ ID NO : 216), Figure 218 (SEQ ID NO : 218), Figure 220 (SEQ ID NO : 220), Figure 222 (SEQ ID NO : 222), Figure (SEQ ID NO : 224), Figure 226 (SEQ ID NO : 226), Figure 228 (SEQ ID NO : 228), Figure 230 (SEQ ID NO : 230), Figure 232 (SEQ ID NO : 234 (SEQ ID NO : 234), Figure 236 (SEQ ID NO : 236), Figure 238 (SEQ ID NO : 238), Figure 240 (SEQ ID NO : 240), Figure 242 (SEQ ID NO : 242), Figure 244 (SEQ ID NO : 244), Figure 246 (SEQ ID NO : 246), Figure 248 (SEQ ID NO : 248), Figure 250 (SEQ ID NO : 250), Figure 252 (SEQ ID NO : 252), Figure 254 (SEQ ID NO : 254), Figure 256 (SEQ ID NO : 256), Figure 258 (SEQ ID NO : 258), Figure 260 (SEQ ID NO : 260), Figure 262 (SEQ ID NO : 262), Figure 264 (SEQ ID NO : 264), Figure 266 (SEQ ID NO : 266), Figure 268 (SEQ ID NO : 268), Figure 270 (SEQ ID NO : 270), Figure 272 (SEQ ID NO : 272), Figure 274 (SEQ ID NO : 274), Figure 276 (SEQ ID NO : 276), Figure 278 (SEQ ID NO : Figure 280 (SEQ ID NO : 280), Figure 282 (SEQ ID NO : 282), Figure 284 (SEQ ID NO : 284),. Figure 286 (SEQ ID NO : 286), Figure 288 (SEQ ID NO : Figure 290 (SEQ ID NO : 290), Figure 292 (SEQ ID NO : 292), Figure 294 (SEQ ID NO : 294), Figure 296 (SEQ ID NO : 296), Figure 298 (SEQ ID NO : 298), Figure 300 (SEQ ID NO : 300), Figure 302 (SEQ ID NO : 302), Figure 304 (SEQ ID NO : 304), Figure 306 (SEQ ID NO : 306), Figure 308 (SEQ ID NO : 308), Figure 310 (SEQ ID NO : 310), Figure 312 (SEQ ID NO : 312), Figure 314 (SEQ ID NO : 314), Figure 316 (SEQ ID NO : 316), Figure 318 (SEQ ID NO : 318), Figure 320 (SEQ ID NO : 320), Figure 322 (SEQ ID NO : 322), Figure 324 (SEQ ID NO : 324), Figure 326 (SEQ ID NO : 326), Figure (SEQ ID NO : 328), Figure 330 (SEQ ID NO : 330), Figure 332 (SEQ ID NO : 332), Figure 334 (SEQ ID NO : 334), Figure 336 (SEQ ID NO : 336), Figure 338 (SEQ ID NO : 338), Figure 340 (SEQ ID NO : 340), Figure 342 (SEQ ID NO : 342), Figure 344 (SEQ ID NO : 344), Figure 346 (SEQ ID NO : 346), Figure 348 (SEQ ID NO : 348), Figure 350 (SEQ ID NO : 350), Figure 352 (SEQ ID NO : 352), Figure 354 (SEQ ID NO : 354), Figure 356 (SEQ ID NO : 356), Figure 358 (SEQ ID NO : 358), Figure 360 (SEQ ID NO : 360), Figure 362 (SEQ ID NO : 362), Figure 364 (SEQ ID NO : 364), Figure 366 (SEQ ID NO : 366), Figure 368 (SEQ ID NO : Figure 370 (SEQ ID NO : 370), Figure 372 (SEQ ID NO : 372), Figure 374 (SEQ ID NO : 374), Figure 376 (SEQ ID NO : 376), Figure 378 (SEQ ID NO : Figure 380 (SEQ ID NO : 380), Figure 382 (SEQ ID NO : 382), Figure 384 (SEQ ID NO : 384), Figure (SEQ ID NO : 386), Figure 388 (SEQ ID NO : 388), Figure 390 (SEQ ID NO : 390), Figure 392 (SEQ ID NO : 392), Figure 394 (SEQ ID NO : 394), Figure 396 (SEQ ID NO : 396), Figure 398 (SEQ ID NO : 398), Figure 400 (SEQ ID NO : 400), Figure 402 (SEQ ID NO : 402), Figure 404 (SEQ NO : 404), Figure 406 (SEQ ID NO : 406), Figure 408 (SEQ ID NO : 408), Figure 410 (SEQ ID NO : 410), Figure 412 (SEQ ID NO : 412), Figure 414 (SEQ ID NO : 414), Figure 416 (SEQ ID NO : 416), Figure 418 (SEQ ID NO : 418), Figure 420 (SEQ ID NO : 420), Figure 422 (SEQ ID NO : 422), Figure 424 (SEQ ID NO : 424), Figure 426 (SEQ ID NO : 426), Figure 428 (SEQ ID NO : Figure 430 (SEQ ID NO : 430), Figure 432 (SEQ ID NO : 432), Figure 434 (SEQ ID NO : 434), Figure 436 (SEQ ID NO : 436), Figure 438 (SEQ ID NO : 438), Figure 440 (SEQ ID NO : 440), Figure 442 (SEQ ID NO : 442), Figure 444 (SEQ ID NO : 444), Figure 446 (SEQ ID NO : 446), Figure 448 (SEQ ID NO : 448), Figure 450 (SEQ ID NO : 450), Figure 452 (SEQ ID NO : 452), Figure 454 (SEQ ID NO : 454), Figure 456 (SEQ ID NO : 456), Figure 458 (SEQ ID NO : 458), Figure 460 (SEQ ID NO : 460), Figure 462 (SEQ ID NO : 462), Figure 464 (SEQ ID NO : 464), Figure 466 (SEQ ID NO : 466), Figure 468 (SEQ ID NO : 468), Figure 470 (SEQ ID NO : 470), Figure 472 (SEQ ID NO : 472), Figure 474 (SEQ ID NO : 474), Figure 476 (SEQ ID NO : 476), Figure 478 (SEQ ID NO : 478), Figure 480 (SEQ ID NO : 480), Figure 482 (SEQ ID NO : 482), Figure 484 (SEQ ID NO : 484), Figure 486 (SEQ ID NO : 486), Figure 488 (SEQ ID NO : Figure 490 (SEQ ID NO : 490), Figure 492

(SEQ ID NO : 492), Figure 494 (SEQ ID NO : 494), Figure 496 (SEQ ID NO : 496), Figure 498 (SEQ ID NO : 498), Figure 500 (SEQ ID NO : 500), Figure 502 (SEQ ID NO : 502), Figure 504 (SEQ ID NO : 504), Figure 506 (SEQ ID NO : 506), Figure 508 (SEQ ID NO : 508), Figure 510 (SEQ ID NO : 510), Figure 512 (SEQ ID NO : 512), Figure 514 (SEQ ID NO : 514), Figure 516 (SEQ ID NO : 516), Figure 518 (SEQ ID NO : 518), Figure 520 (SEQ ID NO : 520), Figure 522 (SEQ ID NO : 522), Figure 524 (SEQ ID NO : 524), Figure 526 (SEQ ID NO : 526), Figure 528 (SEQ ID NO : 528), Figure 530 (SEQ ID NO : 530), Figure 532 (SEQ ID NO : 532), Figure 534 (SEQ ID NO : 534), Figure 536 (SEQ ID NO : 536), Figure 538 (SEQ ID NO : 538), Figure 540 (SEQ ID NO : 540), Figure 542 (SEQ ID NO : 542), Figure 544 (SEQ ID NO : 544), Figure 546 (SEQ ID NO : 546), Figure (SEQ ID NO : 548), Figure 550 (SEQ ID NO : 550), Figure 552 (SEQ ID NO : 552), Figure 554 (SEQ ID NO : 554), Figure 556 (SEQ ID NO : 556), Figure 558 (SEQ ID NO : 558), Figure 560 (SEQ ID NO : 560), Figure 562 (SEQ ID NO : 562), Figure 564 (SEQ ID NO : 564), Figure 566 (SEQ ID NO : 566), Figure 568 (SEQ ID NO : 568), Figure 570 (SEQ ID NO : 570), Figure 572 (SEQ ID NO : 572), Figure 574 (SEQ ID NO : 574), Figure 576 (SEQ ID NO : 576), Figure 578 (SEQ ID NO : 578), Figure 580 (SEQ ID NO : 580), Figure 582 (SEQ ID NO : 582), Figure 584 (SEQ ID NO : 584), Figure 586 (SEQ ID NO : Figure 588 (SEQ ID NO : 588), Figure 590 (SEQ ID NO : 590), Figure 592 (SEQ ID NO : 592), Figure 594 (SEQ ID NO : 594), Figure 596 (SEQ ID NO : 596), Figure 598 (SEQ ID NO : 598), Figure 600 (SEQ ID NO : 600), Figure 602 (SEQ ID NO : 602), Figure 604 (SEQ ID NO : 604), Figure 606 (SEQ ID NO : 606), Figure 608 (SEQ ID NO : 608), or Figure 610 (SEQ ID NO : 610), lacking its associated signal peptide (b) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO : 2), Figure 4 (SEQ ID NO : 6 (SEQ ID NO : 6), Figure 8 (SEQ ID NO : 8), Figure 10 (SEQ ID NO : 10), Figure 12 (SEQ ID NO : 12), Figure 14 (SEQ ID NO : 14), Figure 16 (SEQ ID NO : 16), Figure 18 (SEQ ID NO : 18), Figure 20 (SEQ ID NO : 20), Figure 22 (SEQ ID NO : 22), Figure 24 (SEQ ID NO : 24), Figure 26 (SEQ ID NO : 26), Figure 28 (SEQ ID NO : 28), Figure 30 (SEQ ID NO : 30), Figure 32 (SEQ ID NO : 32), Figure 34 (SEQ ID NO : 34), Figure 36 (SEQ ID NO : 36), Figure 38 (SEQ ID NO : 38), Figure 40 (SEQ ID NO : 40), Figure 42 (SEQ ID NO : 42), Figure 44 (SEQ ID NO : 44), Figure 46 (SEQ ID NO : 46), Figure 48 (SEQ ID NO : 48), Figure 50 (SEQ ID NO : 50), Figure 52 (SEQ ID NO : 52), Figure 54 (SEQ ID NO : 54), Figure 56 (SEQ ID NO : 56), Figure 58 (SEQ ID NO : 58), Figure 60 (SEQ ID NO : 60), Figure 62 (SEQ ID NO : 62), Figure 64 (SEQ ID NO : 64), Figure 66 (SEQ ID NO : 66), Figure (SEQ ID NO : 68), Figure 70 (SEQ ID NO : 70), Figure 72 (SEQ ID NO : 72), Figure 74 (SEQ ID NO : 74), Figure 76 (SEQ ID NO : 76), Figure 78 (SEQ ID NO : 78), Figure 80 (SEQ ID NO : 80), Figure 82 (SEQ ID NO : 82), Figure 84 (SEQ ID NO : 84), Figure 86 (SEQ ID NO : 86), Figure (SEQ ID NO : 88), Figure 90 (SEQ ID NO : 90), Figure 92 (SEQ ID NO : 92), Figure 94 (SEQ ID NO : 94), Figure 96 (SEQ ID NO : 96), Figure 98 (SEQ ID NO : 98), Figure 100 (SEQ ID NO : 100), Figure 102 (SEQ ID NO : 102), Figure 104 (SEQ ID NO : 104), Figure 106 (SEQ ID NO : 106), Figure 108 (SEQ ID NO : 108), Figure 110 (SEQ ID NO : Figure 112 (SEQ ID NO : 112), Figure 114 (SEQ ID NO : 114), Figure 116 (SEQ ID NO : 116), Figure 118 (SEQ ID NO : 118), Figure 120 (SEQ ID NO : 120), Figure 122 (SEQ ID NO : 122), Figure 124 (SEQ ID NO : 124), Figure 126 : 126), Figure 128 (SEQ ID NO : 128), Figure 130 (SEQ ID NO : 130), Figure 132 (SEQ ID NO : 132), Figure 134 (SEQ ID NO : 134), Figure 136 (SEQ ID NO : 136), Figure 138 (SEQ ID NO : 138), Figure (SEQ ID NO : 140), Figure 142 (SEQ ID NO : 142), Figure 144 (SEQ ID NO : 144), Figure 146 (SEQ ID NO : 146), Figure 148 (SEQ ID NO : 148), Figure 150 (SEQ ID NO : 150), Figure 152 (SEQ ID NO : 152), Figure 154 : 154), Figure 156 (SEQ ID NO : 156), Figure 158 (SEQ ID NO : 158), Figure 160 (SEQ ID NO : 160), Figure 162 (SEQ ID NO : 162), Figure 164 (SEQ ID NO : 164), Figure 166 (SEQ ID NO : 166), Figure 168 (SEQ ID NO : 168), Figure 170 (SEQ ID NO : 170), Figure 172 (SEQ ID NO : 172), Figure 174 (SEQ ID NO : 174), Figure 176 (SEQ ID NO : 176), Figure 178 (SEQ ID NO : 178), Figure 180 (SEQ ID NO : 180), Figure 182 (SEQ ID NO : 182), Figure 184 (SEQ ID NO : 184), Figure 186 (SEQ ID NO : 186), Figure 188 (SEQ ID NO : 188), Figure 190 (SEQ ID NO : Figure 192 (SEQ ID NO : 192), Figure 194 (SEQ ID NO : 194), Figure 196 (SEQ ID NO : 196), Figure 198 (SEQ ID NO : 198), Figure 200 (SEQ ID NO : 200), Figure 202 (SEQ ID NO : 202), Figure 204 (SEQ ID NO : 204), Figure 206 (SEQ ID NO : 206), Figure 208 (SEQ ID NO : 208), Figure 210 : 210), Figure

212 : 212), Figure 214 (SEQ ID NO : 214), Figure 216 (SEQ ID NO : Figure 218 (SEQ ID NO : 218), Figure 220 (SEQ ID NO : 220), Figure 222 (SEQ ID NO : 222), Figure 224 (SEQ ID NO : 224), Figure 226 (SEQ ID NO : 226), Figure 228 (SEQ ID NO : 228), Figure 230 (SEQ ID NO : 230), Figure 232 (SEQ ID NO : 232), Figure 234 (SEQ ID NO : 234), Figure 236 (SEQ ID NO : 236), Figure 238 : 238), Figure 240 (SEQ ID NO : 240), Figure 242 (SEQ ID NO : 242), Figure 244 (SEQ ID NO : 244), Figure 246 (SEQ ID NO : 246), Figure 248 (SEQ ID NO : 248), Figure 250 (SEQ ID NO : 250), Figure 252 (SEQ ID NO : 252), Figure 254 (SEQ ID NO : 254), Figure 256 (SEQ ID NO : 256), Figure (SEQ ID NO : 258), Figure 260 (SEQ ID NO : 260), Figure 262 (SEQ ID NO : 262), Figure 264 (SEQ ID NO : 264), Figure 266 (SEQ ID NO : 266), Figure 268 (SEQ ID NO : 268), Figure 270 (SEQ ID NO : 270), Figure 272 (SEQ ID NO : 272), Figure 274 (SEQ ID NO : 274), Figure 276 (SEQ ID NO : 276), Figure 278 (SEQ ID NO : 278), Figure 280 (SEQ ID NO : 280), Figure 282 (SEQ ID NO : 282), Figure 284 (SEQ ID NO : 284), Figure 286 (SEQ ID NO : 286), Figure 288 (SEQ ID NO : Figure 290 (SEQ ID NO : 290), Figure 292 (SEQ ID NO : 292), Figure 294 : 294), Figure 296 (SEQ ID NO : 296), Figure 298 (SEQ ID NO : 298), Figure 300 (SEQ ID NO : 300), Figure 302 (SEQ ID NO : 302), Figure 304 (SEQ ID NO : 304), Figure 306 (SEQ ID NO : 306), Figure 308 : 308), Figure 310 (SEQ ID NO : 310), Figure 312 (SEQ ID NO : 312), Figure 314 (SEQ ID NO : 314), Figure 316 (SEQ ID NO : 316), Figure 318 (SEQ ID NO : 318), Figure 320 (SEQ ID NO : 320), Figure 322 : 322), Figure 324 : 324), Figure 326 (SEQ ID NO : 326), Figure 328 (SEQ ID NO : 328), Figure 330 (SEQ ID NO : 330), Figure 332 (SEQ ID NO : 332), Figure 334 (SEQ ID NO : 334), Figure 336 : 336), Figure 338 (SEQ ID NO : 338), Figure 340 (SEQ ID NO : 340), Figure 342 (SEQ ID NO : 342), Figure 344 (SEQ ID NO : 344), Figure 346 (SEQ ID NO : 346), Figure 348 (SEQ ID NO : Figure 350 (SEQ ID NO : 350), Figure 352 (SEQ ID NO : 352), Figure 354 (SEQ ID NO : 354), Figure 356 (SEQ ID NO : 356), Figure 358 (SEQ ID NO : 358), Figure 360 (SEQ ID NO : 360), Figure 362 (SEQ ID NO : 362), Figure 364 (SEQ ID NO : 364), Figure 366 (SEQ ID NO : 366), Figure 368 (SEQ ID NO : Figure 370 (SEQ ID NO : 370), Figure 372 (SEQ ID NO : 372), Figure 374 (SEQ ID NO : 374), Figure 376 (SEQ ID NO : 376), Figure 378 (SEQ ID NO : 378), Figure 380 (SEQ ID NO : 380), Figure 382 (SEQ ID NO : Figure 384 (SEQ ID NO : 384), Figure 386 (SEQ ID NO : Figure 388 (SEQ ID NO : Figure 390 (SEQ ID NO : 390), Figure 392 (SEQ ID NO : 392), Figure 394 (SEQ ID NO : 394), Figure 396 (SEQ ID NO : 396), Figure 398 (SEQ ID NO : 398), Figure 400 (SEQ ID NO : 400), Figure 402 (SEQ ID NO : 402), Figure 404 (SEQ ID NO : 404), Figure 406 (SEQ ID NO : 406), Figure 408 (SEQ ID NO : 408), Figure 410 (SEQ ID NO : 410), Figure 412 (SEQ ID NO : 412), Figure 414 (SEQ ID NO : 414), Figure 416 (SEQ ID NO : 416), Figure 418 (SEQ ID NO : Figure 420 (SEQ ID NO : 420), Figure 422 (SEQ ID NO : 422), Figure 424 (SEQ ID NO : 424), Figure 426 (SEQ ID NO : 426), Figure 428 (SEQ ID NO : 428), Figure 430 (SEQ ID NO : 430), Figure 432 (SEQ ID NO : 432), Figure 434 (SEQ ID NO : 434), Figure 436 (SEQ ID NO : 436), Figure 438 (SEQ ID NO : 438), Figure 440 (SEQ ID NO : 440), Figure 442 (SEQ ID NO : 442), Figure 444 (SEQ ID NO : 444), Figure 446 (SEQ ID NO : 446), Figure 448 (SEQ ID NO : 448), Figure 450 (SEQ ID NO : 450), Figure 452 (SEQ ID NO : 452), Figure 454 (SEQ ID NO : 454), Figure 456 (SEQ ID NO : 456), Figure 458 (SEQ ID NO : 458), Figure 460 (SEQ ID NO : 460), Figure 462 (SEQ ID NO : 462), Figure 464 (SEQ ID NO : 464), Figure 466 (SEQ ID NO : 466), Figure 468 (SEQ ID NO : 468), Figure 470 (SEQ ID NO : 470), Figure 472 (SEQ ID NO : 472), Figure 474 (SEQ ID NO : 474), Figure 476 (SEQ ID NO : 476), Figure 478 (SEQ ID NO : 478), Figure 480 (SEQ ID NO : 480), Figure (SEQ ID NO : 482), Figure 484 (SEQ ID NO : 484), Figure 486 (SEQ ID NO : 486), Figure 488 (SEQ ID NO : 488), Figure 490 (SEQ ID NO : 490), Figure 492 (SEQ ID NO : 492), Figure 494 (SEQ ID NO : 494), Figure 496 (SEQ ID NO : 496), Figure 498 (SEQ ID NO : 498), Figure 500 (SEQ ID NO : 500), Figure 502 (SEQ ID NO : 502), Figure 504 (SEQ ID NO : 504), Figure 506 (SEQ ID NO : 506), Figure 508 (SEQ ID NO : 508), Figure 510 (SEQ ID NO : 510), Figure 512 (SEQ ID NO : 512), Figure 514 (SEQ ID NO : 514), Figure 516 (SEQ ID NO : 516), Figure 518 (SEQ ID NO : 518), Figure 520 (SEQ ID NO : 520), Figure 522 (SEQ ID NO : 522), Figure 524 (SEQ ID NO : 524), Figure 526 (SEQ ID NO : 526), Figure 528 (SEQ ID NO : 528), Figure 530 (SEQ ID NO : 530), Figure 532 (SEQ ID NO : 532), Figure 534 (SEQ ID NO : 534), Figure 536 (SEQ ID NO : 536), Figure 538 (SEQ ID NO : 538), Figure 540 (SEQ ID NO : 540), Figure 542 (SEQ ID NO : 542), Figure 544 (SEQ

ID NO : 544), Figure 546 (SEQ ID NO : 546), Figure 548 (SEQ ID NO : 548), Figure 550 (SEQ ID NO : 550), Figure 552 (SEQ ID NO : 552), Figure 554 (SEQ ID NO : 554), Figure 556 (SEQ ID NO : 556), Figure 558 (SEQ ID NO : 558), Figure 560 (SEQ ID NO : 560), Figure 562 (SEQ ID NO : 562), Figure 564 (SEQ ID NO : 564), Figure 566 (SEQ ID NO : 566), Figure 568 (SEQ ID NO : 568), Figure 570 (SEQ ID NO : 570), Figure 572 (SEQ ID NO : 572), Figure 574 (SEQ ID NO : 574), Figure 576 (SEQ ID NO : 576), Figure 578 (SEQ ID NO : 578), Figure 580 (SEQ ID NO : 580), Figure 582 (SEQ ID NO : 582), Figure 584 (SEQ ID NO : 584), Figure 586 (SEQ ID NO : 586), Figure 588 (SEQ ID NO : 588), Figure 590 (SEQ ID NO : 590), Figure 592 (SEQ ID NO : 592), Figure 594 (SEQ ID NO : 594), Figure 596 (SEQ ID NO : 596), Figure 598 (SEQ ID NO : 598), Figure 600 (SEQ ID NO : 600), Figure 602 (SEQ ID NO : 602), Figure 604 (SEQ ID NO : 604), Figure 606 (SEQ ID NO : 606), Figure 608 (SEQ ID NO : or Figure 610 (SEQ ID NO : 610), with its associated signal peptide ; or (c) an amino acid sequence of an extracellular domain of the polypeptide shown in Figure 2 (SEQ ID NO : 2), Figure 4 (SEQ ID NO : 4), Figure 6 (SEQ ID NO : 6), Figure 8 (SEQ ID NO : 8), Figure 10 (SEQ NO : 10), Figure 12 (SEQ ID NO : 12), Figure 14 (SEQ ID NO : 14), Figure 16 (SEQ ID NO : 16), Figure 18 (SEQ ID NO : 18), Figure 20 (SEQ ID NO : 20), Figure 22 (SEQ ID NO : 22), Figure 24 (SEQ ID NO : 24), Figure 26 (SEQ ID NO : 26), Figure 28 (SEQ ID NO : 28), Figure 30 (SEQ ID NO : 30), Figure 32 (SEQ ID NO : 32), Figure 34 (SEQ ID NO : 34), Figure 36 (SEQ ID NO : 36), Figure 38 (SEQ ID NO : Figure 40 (SEQ ID NO : 40), Figure 42 (SEQ ID NO : 42), Figure 44 (SEQ ID NO : 44), Figure 46 (SEQ ID NO : 46), Figure 48 (SEQ ID NO : 48), Figure 50 (SEQ ID NO : 50), Figure 52 (SEQ ID NO : 52), Figure 54 (SEQ ID NO : 54), Figure 56 (SEQ ID NO : 56), Figure 58 (SEQ ID NO : 58), Figure 60 (SEQ ID NO : 60), Figure 62 (SEQ ID NO : 62), Figure 64 (SEQ ID NO : 64), Figure 66 (SEQ ID NO : 66), Figure 68 (SEQ ID NO : 68), Figure 70 (SEQ ID NO : 70), Figure 72 (SEQ ID NO : 72), Figure 74 (SEQ ID NO : 74), Figure 76 (SEQ ID NO : 76), Figure 78 (SEQ NO : 78), Figure 80 (SEQ ID NO : 80), Figure 82 (SEQ ID NO : 82), Figure 84 (SEQ ID NO : 84), Figure 86 (SEQ ID NO : 86), Figure 88 (SEQ ID NO : 88), Figure 90 (SEQ ID NO : 90), Figure 92 (SEQ ID NO : 92), Figure 94 (SEQ ID NO : 94), Figure 96 (SEQ ID NO : 96), Figure 98 (SEQ ID NO : 98), Figure 100 (SEQ ID NO : 100), Figure 102 (SEQ ID NO : 102), Figure 104 (SEQ ID NO : 104), Figure 106 (SEQ ID NO : 106), Figure (SEQ ID NO : 108), Figure (SEQ ID NO : Figure 112 (SEQ ID NO : Figure 114 (SEQ ID NO : 114), Figure 116 (SEQ ID NO : 116), Figure 118 : 118), Figure 120 : 120), Figure 122 : 122), Figure 124 (SEQ ID NO : 124), Figure 126 (SEQ ID NO : 126), Figure 128 (SEQ ID NO : 128), Figure 130 (SEQ ID NO : 130), Figure 132 (SEQ ID NO : 132), Figure 134 (SEQ ID NO : 134), Figure 136 (SEQ ID NO : 136), Figure (SEQ ID NO : 138), Figure 140 (SEQ ID NO : 140), Figure 142 (SEQ ID NO : 142), Figure 144 (SEQ ID NO : 144), Figure 146 (SEQ ID NO : 146), Figure 148 (SEQ ID NO : Figure 150 (SEQ ID NO : 150), Figure 152 (SEQ ID NO : 152), Figure 154 (SEQ ID NO : 154), Figure 156 (SEQ ID NO : 156), Figure 158 (SEQ ID NO : 158), Figure 160 (SEQ ID NO : 160), Figure 162 (SEQ ID NO : 162), Figure 164 (SEQ ID NO : 164), Figure 166 (SEQ ID NO : 166), Figure 168 (SEQ ID NO : 168), Figure 170 (SEQ ID NO : 170), Figure 172 (SEQ ID NO : 172), Figure 174 (SEQ ID NO : 174), Figure 176 (SEQ ID NO : 176), Figure 178 (SEQ ID NO : 178), Figure 180 (SEQ ID NO : 180), Figure (SEQ ID NO : 182), Figure 184 (SEQ ID NO : 184), Figure 186 (SEQ ID NO : 186), Figure 188 (SEQ ID NO : 188), Figure 190 (SEQ ID NO : 190), Figure 192 (SEQ ID NO : 192), Figure 194 (SEQ ID NO : 194), Figure 196 (SEQ ID NO : 196), Figure 198 (SEQ ID NO : 198), Figure 200 (SEQ ID NO : 200), Figure 202 (SEQ ID NO : 202), Figure 204 (SEQ ID NO : 204), Figure 206 (SEQ ID NO : 206), Figure 208 (SEQ ID NO : 208), Figure 210 (SEQ ID NO : 210), Figure 212 (SEQ ID NO : 212), Figure 214 (SEQ ID NO : 214), Figure 216 (SEQ ID NO : 216), Figure 218 (SEQ ID NO : Figure 220 (SEQ ID NO : 220), Figure 222 (SEQ ID NO : 222), Figure 224 (SEQ ID NO : 224), Figure 226 (SEQ ID NO : 226), Figure 228 (SEQ ID NO : 228), Figure 230 (SEQ ID NO : 230), Figure 232 (SEQ ID NO : 232), Figure 234 (SEQ ID NO : 234), Figure 236 (SEQ ID NO : 236), Figure 238 (SEQ ID NO : 238), Figure 240 (SEQ ID NO : 240), Figure 242 (SEQ ID NO : 242), Figure 244 (SEQ ID NO : 244), Figure 246 (SEQ ID NO : 246), Figure 248 (SEQ ID NO : 248), Figure 250 (SEQ ID NO : 250), Figure 252 (SEQ ID NO : 252), Figure 254 (SEQ ID NO : 254), Figure 256 (SEQ ID NO : 256), Figure 258 (SEQ ID NO : 258), Figure 260 (SEQ ID NO : 260), Figure 262 (SEQ ID NO : 262), Figure 264 (SEQ ID NO : 264),

Figure 266 (SEQ ID NO : 266), Figure 268 (SEQ ID NO : 268), Figure 270 (SEQ ID NO : 270), Figure 272 (SEQ ID NO : 272), Figure 274 (SEQ ID NO : 274), Figure 276 (SEQ ID NO : 276), Figure 278 (SEQ ID NO : 278), Figure 280 (SEQ ID NO : 280), Figure 282 (SEQ ID NO : 282), Figure 284 (SEQ ID NO : 284), Figure 286 (SEQ ID NO : 286), Figure 288 (SEQ ID NO : 288), Figure 290 (SEQ ID NO : 290), Figure 292 (SEQ ID NO : 292), Figure 294 (SEQ ID NO : 294), Figure 296 (SEQ ID NO : 296), Figure 298 (SEQ ID NO : 298), Figure 300 (SEQ ID NO : 300), Figure 302 (SEQ ID NO : 302), Figure 304 (SEQ ID NO : 304), Figure 306 (SEQ ID NO : 306), Figure (SEQ ID NO : 308), Figure 310 (SEQ ID NO : 310), Figure 312 (SEQ ID NO : 312), Figure 314 (SEQ ID NO : 314), Figure 316 (SEQ ID NO : 316), Figure 318 (SEQ ID NO : 318), Figure 320 (SEQ ID NO : 320), Figure 322 (SEQ ID NO : 322), Figure 324 (SEQ ID NO : 324), Figure 326 (SEQ ID NO : 326), Figure 328 (SEQ ID NO : 328), Figure 330 (SEQ ID NO : 330), Figure 332 (SEQ ID NO : 332), Figure 334 (SEQ ID NO : 334), Figure 336 (SEQ ID NO : 336), Figure 338 (SEQ ID NO : 338), Figure 340 (SEQ ID NO : 340), Figure 342 (SEQ ID NO : 342), Figure 344 (SEQ ID NO : 344), Figure 346 (SEQ ID NO : 346), Figure 348 (SEQ ID NO : 348), Figure 350 (SEQ ID NO : 350), Figure 352 (SEQ ID NO : 352), Figure 354 (SEQ ID NO : 354), Figure 356 (SEQ ID NO : 356), Figure 358 (SEQ ID NO : 358), Figure 360 (SEQ ID NO : 360), Figure 362 (SEQ ID NO : 362), Figure 364 (SEQ ID NO : 364), Figure 366 (SEQ ID NO : 366), Figure 368 (SEQ ID NO : 368), Figure 370 (SEQ ID NO : 370), Figure 372 (SEQ ID NO : 372), Figure 374 (SEQ ID NO : 374), Figure 376 (SEQ ID NO : 376), Figure 378 (SEQ ID NO : 378), Figure 380 (SEQ ID NO : 380), Figure 382 (SEQ ID NO : 382), Figure 384 (SEQ ID NO : 384), Figure 386 (SEQ ID NO : 386), Figure 388 (SEQ ID NO : 388), Figure 390 (SEQ ID NO : 390), Figure 392 (SEQ ID NO : 392), Figure 394 (SEQ ID NO : 394), Figure 396 (SEQ ID NO : 396), Figure 398 (SEQ ID NO : Figure 400 (SEQ ID NO : 400), Figure 402 (SEQ ID NO : 402), Figure 404 (SEQ ID NO : 404), Figure 406 (SEQ ID NO : 406), Figure 408 (SEQ ID NO : 408), Figure 410 (SEQ ID NO : 410), Figure 412 (SEQ ID NO : 412), Figure 414 (SEQ ID NO : 414), Figure 416 (SEQ ID NO : 416), Figure (SEQ ID NO : 418), Figure 420 (SEQ ID NO : 420), Figure 422 (SEQ ID NO : 422), Figure 424 (SEQ ID NO : 424), Figure 426 (SEQ ID NO : 426), Figure 428 (SEQ ID NO : 428), Figure 430 (SEQ ID NO : 430), Figure 432 (SEQ ID NO : 432), Figure 434 (SEQ ID NO : 434), Figure 436 (SEQ ID NO : 436), Figure 438 (SEQ ID NO : 438), Figure 440 (SEQ ID NO : 440), Figure 442 (SEQ ID NO : 442), Figure 444 (SEQ ID NO : 444), Figure 446 (SEQ ID NO : 446), Figure 448 (SEQ ID NO : 448), Figure 450 (SEQ ID NO : 450), Figure 452 (SEQ ID NO : 452), Figure 454 (SEQ ID NO : Figure 456 (SEQ ID NO : 456), Figure 458 (SEQ ID NO : 458), Figure 460 (SEQ ID NO : 460), Figure 462 (SEQ ID NO : 462), Figure 464 (SEQ ID NO : 464), Figure 466 (SEQ ID NO : 466), Figure 468 (SEQ ID NO : 468), Figure 470 (SEQ ID NO : 470), Figure 472 (SEQ ID NO : 472), Figure 474 (SEQ ID NO : 474), Figure 476 (SEQ ID NO : 476), Figure 478 (SEQ ID NO : 478), Figure 480 (SEQ ID NO : 480), Figure 482 (SEQ ID NO : 482), Figure 484 (SEQ ID NO : 484), Figure 486 (SEQ ID NO : 486), Figure 488 (SEQ ID NO : 488), Figure 490 (SEQ ID NO : 490), Figure 492 (SEQ ID NO : 492), Figure 494 (SEQ ID NO : 494), Figure 496 (SEQ ID NO : 496), Figure 498 (SEQ ID NO : 498), Figure 500 (SEQ ID NO : 500), Figure 502 (SEQ ID NO : 502), Figure 504 (SEQ ID NO : 504), Figure 506 (SEQ ID NO : 506), Figure 508 (SEQ ID NO : 508), Figure 510 (SEQ ID NO : 510), Figure 512 (SEQ ID NO : 512), Figure 514 (SEQ ID NO : 514), Figure 516 (SEQ ID NO : 516), Figure 518 (SEQ ID NO : 518), Figure 520 (SEQ ID NO : 520), Figure 522 (SEQ ID NO : 522), Figure 524 (SEQ ID NO : 524), Figure 526 (SEQ ID NO : 526), Figure 528 (SEQ ID NO : 528), Figure 530 (SEQ ID NO : 530), Figure 532 (SEQ ID NO : 532), Figure 534 (SEQ ID NO : 534), Figure 536 (SEQ ID NO : 536), Figure 538 (SEQ ID NO : 538), Figure 540 (SEQ ID NO : 540), Figure 542 (SEQ ID NO : 542), Figure 544 (SEQ ID NO : 544), Figure 546 (SEQ ID NO : 546), Figure 548 (SEQ ID NO : Figure 550 (SEQ ID NO : 550), Figure 552 (SEQ ID NO : Figure 554 (SEQ ID NO : 554), Figure 556 (SEQ ID NO : 556), Figure 558 (SEQ ID NO : 558), Figure 560 (SEQ ID NO : 560), Figure 562 (SEQ ID NO : 562), Figure 564 (SEQ ID NO : 564), Figure 566 (SEQ ID NO : 566), Figure 568 (SEQ ID NO : 568), Figure 570 (SEQ ID NO : 570), Figure 572 (SEQ ID NO : 572), Figure 574 (SEQ ID NO : 574), Figure 576 (SEQ ID NO : 576), Figure 578 (SEQ ID NO : 578), Figure 580 (SEQ ID NO : 580), Figure 582 (SEQ ID NO : 582), Figure 584 (SEQ ID NO : 584), Figure 586 (SEQ ID NO : 586), Figure 588 (SEQ ID NO : 588), Figure 590 (SEQ

ID NO : 590), Figure 592 (SEQ ID NO : 592), Figure 594 (SEQ ID NO : 594), Figure 596 (SEQ ID NO : 596), Figure 598 (SEQ ID NO : 598), Figure 600 (SEQ ID NO : 600), Figure 602 (SEQ ID NO : 602), Figure 604 (SEQ ID NO : 604), Figure 606 (SEQ ID NO : 606), Figure 608 (SEQ ID NO : 608), or Figure 610 (SEQ ID NO : 610), lacking its associated signal peptide.

20. A method for stimulating the release of from human blood, said method comprising contacting or PR04333 polypeptide, wherein the release of from said blood is stimulated.

21. A method for stimulating the proliferation or differentiation of chondrocyte cells, said method comprising contacting said cells with a PR06029 polypeptide, wherein the proliferation or differentiation of said cells is stimulated.

22. A method for detecting the presence of tumor in an mammal, said method comprising comparing the level of expression of any PRO polypeptide shown in Table 8 in (a) a test sample of cells taken from said mammal and (b) a control sample of normal cells of the same cell type, wherein a higher level of expression of said PRO polypeptide in the test sample as compared to the control sample is indicative of the presence of tumor in said mammal.

23. The method of Claim 22, wherein said tumor is adrenal tumor, lung tumor, colon tumor, breast tumor, prostate tumor, rectal tumor, cervical tumor or liver tumor.

24. An oligonucleotide probe derived from any of the nucleotide sequences shown in the accompanying figures.